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Reviews and perspectives

Evidence that transcranial direct current stimulation (tDCS) generates little-to-no reliable neurophysiologic effect beyond MEP amplitude modulation in healthy human subjects: A systematic review

Jared Cooney Horvath *, Jason D. Forte, Olivia Carter

University of Melbourne, School of Psychological Sciences, Melbourne, VIC, Australia

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ABSTRACT

Background: Transcranial direct current stimulation (tDCS) is a form of neuromodulation that is increasingly being utilized to examine and modify a number of cognitive and behavioral measures. The theoretical mechanisms by which tDCS generates these changes are predicated upon a rather large neurophysiological literature. However, a robust systematic review of this neurophysiological data has not yet been undertaken.

Methods: tDCS data in healthy adults (18–50) from *every* neurophysiological outcome measure reported by at least two different research groups in the literature was collected. When possible, data was pooled and quantitatively analyzed to assess significance. When pooling was not possible, data was qualitatively compared to assess reliability.

Results: Of the 30 neurophysiological outcome measures reported by at least two different research groups, tDCS was found to have a reliable effect on only one: MEP amplitude. Interestingly, the magnitude of this effect has been significantly decreasing over the last 14 years.

Conclusion: Our systematic review does not support the idea that tDCS has a reliable neurophysiological effect beyond MEP amplitude modulation – though important limitations of this review (and conclusion) are discussed. This work raises questions concerning the mechanistic foundations and general efficacy of this device – the implications of which extend to the steadily increasing tDCS psychological literature.

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* Correspondence to: Melbourne School of Psychological Sciences, Redmond Barry Building, University of Melbourne, VIC 3010, Australia.
E-mail address: jared.cooney.horvath@gmail.com (J.C. Horvath).

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1. Introduction

Nearly fifteen years ago, researchers revived a field of research that explores the effects of running a weak electric current between two electrodes placed on the scalp of healthy individuals (Konig and Ankenmuller, 1960; Hamer, 1968; Lolas 1977; Elbert et al., 1981; Nitsche and Paulus, 2000). Dubbing this technique transcranial direct current stimulation (tDCS), experiments showed a marked, time dependent, and polarity specific modulation of neuronal populations underlying the electrodes. Since this initial neurophysiologic finding, a growing number of researchers and clinicians have been exploring the effects of tDCS across a number of cognitive/behavioral domains. Today, the literature suggest tDCS can enhance a number of higher-order cognitions and behaviors ranging from working memory and motor learning to emotional regulation and focused attention (for review: Nitsche and Paulus, 2011). The claims made by cognitive and behavioral tDCS researchers largely depend upon the mechanistic framework suggested by the neurophysiologic data. However, a robust systematic review of the neurophysiologic impact of tDCS has not yet been undertaken. This is something we hope to remedy in this paper.

1.1. tDCS: A brief overview and proposed mechanisms of action

Modern tDCS devices typically consist of an adjustable direct current stimulator and two stimulating electrodes (an anode and a cathode). These electrodes are typically attached to two separate locations on the scalp (either directly or via larger sponge electrodes) and a weak current (0.5–2.0 mA) is run between the electrodes. As this current passes between the electrodes, it is believed a small amount of the current passes through the brain. This current flow is purported to modulate neural activity underneath the electrode and, to a lesser extent, diffuse locations in the brain (Nitsche et al., 2008; for debate: Bikson, 2013).

There are two mechanisms by which tDCS modulates brain activity that are widely accepted in the field. The first proposes tDCS modulates the resting membrane potential of neuronal populations via ionic adjustment of extracellular space. More specifically, neurons proximal to the anode are thought to become hypo-polarized whist neurons near the cathode are thought to become hyper-polarized (Stagg and Nitsche, 2011). This shift in resting membrane potential is believed to occur both *during* stimulation and for a short period of time (<5 min) following stimulation. The second proposes tDCS modulates synaptic activity in a manner akin to long term potentiation (under the anode) and long term depression (under the cathode: Stagg and Nitsche, 2011). This mechanism is believed to be active for an extended period of time (up to 120 min) following the cessation of long-duration (>7 min) stimulation. In this systematic review, we group studies into short- and long-duration stimulation to account for membrane and synaptic effects believed to be triggered by tDCS.

1.2. Systematic review structure

The neurophysiological effects of tDCS have largely been measured utilizing four approaches: transcranial magnetic stimulation (TMS), event related potentials (ERPs), electroencephalographic spectral analyses (EEG), and functional magnetic resonance imaging (fMRI). Accordingly, the methods and results sections (below) will be structured around these modalities. Additionally, the majority of studies exploring the neurophysiological effects of tDCS have utilized a single measure: TMS motor evoked potential (MEP) amplitude. Due to the disproportionately large number of studies exploring this measure, we have decided to dedicate an analysis

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section solely to this measure (rather than combine it with other TMS measures).

1.2.1. Transcranial magnetic stimulation (TMS)

Transcranial magnetic stimulation (TMS) is a device that allows for non-invasive electrical stimulation of localized regions of the cortical surface. Via the rapid passing of a strong electrical current through a coil held against an individual's head, TMS generates an equally rapid fluctuating magnetic field which (via electromagnetic induction) generates a secondary current within the cortex effectively force-firing underlying neuronal populations. Single TMS pulses of sufficient strength to the motor cortical representation of a particular muscle can cause that muscle to activate. Various aspects of muscular activation can be measured (using electromyography: EMG) and analyzed to infer cortical and spinal excitability patterns (Hallett, 2007). As such, TMS evoked muscular responses represent an excellent tool to explore modulation engendered by tDCS. There are several TMS evoked motor outcomes which have been utilized to explore the modulatory effects of tDCS.

1.2.1.1. Motor evoked potential (MEP) amplitude. When a TMS pulse activates a target muscle, the resultant muscular 'twitch' is commonly referred to as a motor evoked potential (MEP). The amplitude of each MEP can be thought of as a measure of the *strength* of the muscular activation. As it is generally accepted that TMS activates pyramidal neurons transynaptically (Rotenberg et al., 2014), TMS generated MEP amplitudes are believed to reflect the excitability of corticocortical circuits. Additionally, MEP amplitudes are reflective of, and can be modulated according to, spinal motorneuron excitability. Accordingly, when utilizing a single TMS pulse intensity, any increase in MEP amplitude is thought to reflect either an increase in synaptic excitability at the level of the motor cortex or the spinal cord- and vice versa (Hallett, 2000).

1.2.1.2. Resting motor threshold (rMT) and active motor threshold (aMT). rMT commonly refers to the minimum intensity of TMS pulse required to elicit a specified number of MEPs (typically 50% response rate) in a *relaxed* muscle. Although synaptic connections at the cortical level doubtless influence this measure, rMT is thought to depend more on axonal membrane excitability (Hallett, 2007). aMT commonly refers to the minimum intensity of TMS pulse required to elicit a specified number of MEPs (typically 50% response rate) in an *activated* muscle (typically voluntary contraction at 15–30%). As muscle contraction elevates the excitability of large groups of cortical neurons and spinal motoneurons, aMT is thought to depend more directly on axonal threshold than rMT (Hallett, 2007).

1.2.1.3. Cortical silent period (cSP). A TMS pulse to the motor cortex typically engenders both an excitatory and inhibitory effect. Whereas the excitatory effect is reflected in the MEP, the inhibitory effect is reflected in a suppression of EMG activity (~100–300 ms) immediately following the MEP; the duration of which constitutes the cSP. The first 50 ms of the cSP are thought to reflect spinal mechanisms, whereas the remaining portion is mediated by cortical inhibition (Cantello et al., 1992).

1.2.1.4. Short interval cortical inhibition (SICI) and intracortical facilitation (ICF). The application of two TMS pulses to the same motor cortical location separated by variable interstimulus intervals (ISIs) is another method for exploring excitatory and inhibitory corticocortical circuits. When the first (conditioning stimulus) and second (test stimulus) TMS pulses are applied with an ISI of 2–6 ms, the second MEP will typically be smaller than the first. This diminution, termed SICI, is thought to reflect axonal refractoriness and GABAergic mediated synaptic inhibition (Nakamura et al., 1997). When the two pulses are applied with an ISI of 7–30 ms, the second MEP will typically be larger than the first. This elevation, termed ICF, is thought to reflect glutamatergic mediated synaptic facilitation. During SICI and ICF paradigms, test pulse MEP amplitudes are typically reported as a percentage of the normalized conditioning pulse MEP amplitudes (Nakamura et al., 1997).

As each of these TMS outcome measures have been utilized to explore the modulatory effects of tDCS, the results of each will be presented in turn.

1.2.2. Event related potential (ERP)

ERPs are specific and reliable neural responses to specific sensory stimuli. These responses can be measured using electroencephalography (EEG). A typical ERP will contain a number of negative and positive peaks occurring within predictable time windows following stimulus onset. The constituent parts of ERPs are thought to reflect brain function. More specifically, peak amplitude is thought to reflect underlying cortical excitability (Handy, 2005). As such, the comparison of ERP amplitudes prior to and following tDCS represents a unique way to measure the modulatory effects of tDCS. Although a number of ERP measures have been explored in the literature, only four have satisfied our inclusion criteria of being replicated by at least two different research groups (for a full list of ERP measures that did not meet this criteria, see Table S1).

1.2.2.1. P100 visual evoked potential (VEP). When an ERP is evoked using visual stimuli (either low or high contrast), the resultant response is termed a VEP. VEPs often include a positive peak ~100 ms post stimulus presentation at the occipital pole. Termed the P100, the amplitudes of this peak has been shown to be highly reliable and sensitive to excitability shifts within individuals at the level of the visual cortex (Di Russo et al., 2002). Q5

1.2.2.2. N20 somatosensory evoked potential (SEP). When an ERP is evoked using a brief sensory stimulus (typically generated on the periphery of the body), the resultant response is termed an SEP. An often utilized method of SEP evocation is the use of electrical stimulation at the median nerve of the wrist. This particular SEP often includes a negative peak ~20 ms post-stimulation near the somatosensory cortex. Termed the N20, the amplitude of this peak has been shown to be highly reliable and sensitive to excitability shifts within individuals at the level of the somatosensory cortex (Emerson et al., 1988).

1.2.2.3. N2 and P2 laser evoked potential (LEP). When an ERP is evoked using a heat generating laser (typically focused on the back of the hand), the resultant response is termed an LEP. Thought to represent neural pain processing, LEPs often include a negative/positive wave ~200 ms post-stimulation near the somatosensory cortex. Termed the N2 and P2 waves (respectively), the amplitudes of these peaks have been shown to be highly reliable and sensitive to excitability shifts in individuals at the level of the somatosensory cortex (Ohara et al., 2004).

1.2.2.4. – Mu/Alpha event related desynchronization (ERD). Although not a singular potential, ERD is a measure of amplitude response across an oscillatory range (see below for additional EEG power spectrum information). Amplitude modulation across unique frequencies has been shown to correlate with unique cognitive and/or behavioral activity. More specifically, the Mu/Alpha frequency (typically 8–13 Hz) over the sensory-motor cortex typically displays large amplitude peaks when a person is at rest. However, these waves attenuate (de-synchronize) during motor

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performance, observation, and imagery – theoretically due to overt or covert activation of the motor system (Guieu et al., 1999). Although this outcome measure may be more comparable to those included in the EEG power spectrum section (below), we have included it here as we were able to analyze it quantitatively.

1.2.3. Electroencephalography (EEG) power spectrum

EEG is an imaging modality used to record the electrical activity of neural groups. Although EEG recordings can be divided into and analyzed according to brief temporal windows (see ERPs, above), long duration EEG analysis allows for the determination of oscillation patterns over-time across the entire brain or within specified neural regions. Oscillatory patterns are typically broken into five different frequency bands: Delta (0–4 Hz), Theta (4–7 Hz), Alpha (7–14 Hz), Beta (15–30 Hz), and Gamma (> 30 Hz). These oscillations represent synchronous activity over diffuse neural networks and the power of each (relative to the others) is thought to correspond to different states of brain function and/or behavior (e.g.: high power in the theta band has been associated with drowsiness and response inhibition: Rowan and Tolunsky, 2003). As such, the unique ratio of oscillatory power prior to and following stimulation whilst individuals undertake varied tasks represents an important method for exploring the modulatory effect of tDCS on diffuse cortical networks.

1.2.4. Functional magnetic resonance imaging (fMRI)

fMRI is used to measure blood oxygen level dependent (BOLD) signals within the brain across time. The hemodynamics measured by fMRI are thought to correspond with neural activity such that an increase of blood flow to a cortical region is thought to be associated with an increase in neural activity within that region (Logothetis et al., 2011). The amount or intensity of BOLD activation prior to and following stimulation can be used to explore the resting firing rate modulatory effects of tDCS both underneath the electrode and across diffuse cortical networks.

1.3. Omitted measures

For a list of TMS, ERP, EEG power spectrum, and fMRI related outcome measures not replicated between at least two research groups (therefore, excluded from this analysis), please see Table S1 in the Supplementary material. Several additional physiological outcome measures (not easily grouped into one of these 4 categories) were also not included in this analysis due to using non-comparable protocols and/or data reporting. Additional protocol details from each of these studies (briefly outlined below) are presented in Table S2 in the Supplementary material.

Although a number of papers have used MRI to explore functional connectivity measures following tDCS to M1 (Polania et al., 2012a, 2012b; Sehm et al., 2013; Stagg et al., 2009b) and the DLPFC (Keeser et al., 2011; Park et al., 2013; Pena-Gomez et al., 2012), the modes of data acquisition, analyses, and reporting conducted by each are dissimilar and difficult to meaningfully compare. For these reasons, we have opted not to include these measures in this systematic review. It is worth noting, however, that Paquette et al. (2011) recently noted that these papers have produced "…to some extent, conflicting results" (p. 2086).

Additionally, four papers have used magnetic resonance spectroscopy (MRS) to explore the neurochemical impact of tDCS (Clark et al., 2011; Rango et al., 2008; Stagg et al., 2011, 2009a). Unfortunately, as each used different and incompatible imaging methodologies and stimulation parameters, we have opted not to include these measures in our systematic. It is worth noting, however, that the only common neurometabolite measure reported between the studies was Glx concentration (a composite measure of glutamate and glutamine). Of the four, two reported a significant effect of tDCS on this measure whilst two reported no effect.

Two papers have explored the impact of tDCS on bioenergetics using Phosphorus MRS (Binkofski et al., 2011; Rae et al., 2013). Unfortunately, the stimulation protocol and outcome measures reported for each were different negating the possibility of a meaningful comparison.

Two papers have explored the effects of tDCS on regional cerebral blood flow using positron emission tomography (Lang et al., 2005; Paquette et al., 2011). Again, as the tDCS protocols utilized by each different significantly, it was not possible to generate a meaningful comparison.

Finally, several recent studies have utilized HD-tDCS and individualized electrode placement based on personal MRI electric current flow models (e.g. – Kuo et al., 2013; Villamar et al., 2013; Borckardt et al., 2012; Clark et al., 2012). Unfortunately, although these new techniques are promising, most studies have utilized clinical population and there is not yet enough data in healthy controls to derive meaningful conclusions. Accordingly, we have omitted these studies from our analysis.

2. Methods

2.1. General

It is common in quantitative analyses of multiple studies to translate the outcome values of each to a common measure before undertaking any comparison (e.g. – effect size or standardized mean difference). In order to obtain a common measure, however, reported outcome values must be compared to a control or sham condition. Unfortunately, the vast majority of numerically analyzable studies included in this systematic review (92 out of 117) did not include a control or sham condition. For this reason, no effect size and/or standard mean difference could be determined. Rather, we maintained the central measure as reported in each paper and obtained weighted means and pooled standard deviations for normalized data at each appropriate time-point post-stimulation. If numerical data was not supplied in the text, averages and variance were extracted from included images (achieved by exporting images to an image editing program, overlaying a standardized grid, and counting relevant values by hand). This visual data extraction process was undertaken by the lead author. When possible, obtained values were run through the statistical tests reported in the representative paper to assess accuracy of the extracted data.

Final values were compared using unpaired Student's *t*-tests (when no SHAM condition was available), and one-way ANOVAs (when a SHAM condition was available) to determine any difference between obtained values. If significance using an ANOVA was established, post-hoc analysis consisted of between condition bonferonni corrected *t*-tests. As each experiment reported varied temporal testing protocols following stimulation (see tables for more specific information), we were unable to run any two-way ANOVAs (using 'time' as a variable).

As noted below, one of the only absolute inclusion criteria for this analysis was that an outcome measure be replicated by at least two different research groups. Examples of non-experimentally based systematic errors reliably influencing the results generated by a single research group can be found in all the sciences, from physics (see Gieryn, 1992), to biology (see Mobley et al., 2013), to medicine (see Osherovich, 2013). We, therefore, chose to exclude measures that have only been replicated by a single research group to ensure all data included in and conclusions generated by this review accurately reflect the effects of tDCS itself, rather than any unique device, protocol, or condition utilized in a

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Table 1
Studies exploring the effects of low and high density tDCS on TMS elicited MEP amplitude of varied muscles at rest.

Paper/# of studies	*N*	tDCS duration	tDCS polarities	DB/NN	Tar.	TMS power/frequency	# of MEPs averaged	*T*(*x*)
Low density (0.02857 mA/cm^2)/very-short duration (< 1 min) – tested muscle at rest								
Nitsche and Paulus (2000)	10	4 s	A, C	–/–	IHM	2 mV MEP/0.25 Hz	12	–
Nitsche et al. (2003a, 2003b)	12	4 s	A, C	–/–	IHM	1 mV MEP/0.1 Hz	15	–
Nitsche et al. (2004)	6	4 s	A, C	–/–	IHM	1 mV MEP/0.1 Hz	15	–
Nitsche et al. (2004)	12	4 s	A, C	–/–	IHM	1 mV MEP/0.1 Hz	15	–
Nitsche et al. (2007/*x*3)	12 (*x*3)	4 s (*x*3)	A, C (*x*3)	–/–	IHM	1 mV MEP/0.1 Hz	15	–
Low density (0.02857 mA/cm^2)/short duration (1–7 min) – tested muscle at rest								
Nitsche and Paulus (2000)	19	7 min	A, C	–/–	IHM	2 mV MEP/0.25 Hz	Continuous	T0 – T10
Nitsche and Paulus (2001)	12	7 min	A	–/–	IHM	1 mV MEP/0.25 Hz	20 bl/15 @ 5 min	T0 – T15
Liebetanz et al. (2002)	11	5 min	A, C	Y/–	IHM	1 mV MEP/0.25 Hz	20 bl/continuous	T0 – T10
Nitsche et al. (2003/*x*2)	12 (*x*2)	5 min (*x*1)7 min (*x*1)	C (*x*2)	–/–	IHM	1 mV MEP/0.25 Hz	20 bl/15 @ 5 min	T0 (*x*1)T0 – T10 (*x*1)
Nitsche et al. (2004)	6	7 min	A, C	–/–	IHM	1 mV MEP/0.25 Hz	20 bl/15 per 5 min	T0 – T15
Nitsche et al. (2004)	9	5 min	A, C	–/–	IHM	1 mV MEP/0.25 Hz	20 bl/continuous	T0 – T10
Quartarone et al. (2004/*x*2)	7 (*x*1) 21 (*x*1)	5 min (*x*2)	A (*x*1) C (*x*1)	–/–	IHM	0.5–1 mV MEP/0.25 Hz	15 @ 10 min	T0, T10 (*x*2)
Nitsche et al. (2007/*x*3)	12 (*x*3)	7 min (*x*3)	A, C (*x*3)	–/–	IHM	1 mV MEP/0.25 Hz	15 @ 5 min	T0-T15
Nitsche et al. (2007)	12	7 min	A, C	–/–	IHM	1 mV MEP/0.25 Hz	20 bl/15 @ 5 min	T0 – T15
Fricke et al. (2011/*x*2)	8 (*x*1) 12 (*x*1)	5 min (*x*1)7 min (*x*1)	A (*x*2)	–/–	IHM	1 mV MEP/0.25 Hz	30 @ 5 min	T0 – T5 (x1)T0-T15 (x1)
Munneke et al. (2011)	10	7 min	C	–/–	IHM	0.5 mV MEP/0.25 Hz	30	T5
Schade et al. (2012/*x*2)	8 (*x*2)	5 min (*x*2)	A, C (*x*2)	Y/–	IHM	1 mV MEP/0.25 Hz	25 bl/75 1 st 5 min/25 @ 5 min	T0 – T15
Rizzo et al. (2014)	10	5 min	A, C	–/–	IHM	0.5–1 mV MEP/0.1 Hz	20 @ 10 min	T0, T10
Low density (0.02857 mA/cm^2)/long duration (> 7 min) – tested muscle at rest								
Nitsche and Paulus (2001)	12 (*x*2)	9 min (*x*1)13 min (*x*1)	A	–/–	IHM	1 mV MEP/0.25 Hz	20 bl/15 @ 5 min	T0 – T60 (*x*2)
Nitsche et al. (2003/*x*2)	10	9 min C/11–13 min A (*x*2)	A, C	–/–	IHM	1 mV MEP/0.25 Hz	20 bl/15 @ 5 min	T0 – T60 (*x*2)
Nitsche et al. (2003)	12	9 min	C	–/–	IHM	1 mV MEP/0.25 Hz	20 bl/15 @ 5 min	T0 – T60
Lang et al. (2004)	8	10 min	A, C	–/–	IHM	150% rMT/0.25 Hz	30	T0
Lang et al. (2004/*x*2)	5 (*x*1) 10 (*x*1)	10 min (*x*2)	A, C (*x*1)A, C, S (*x*1)	–/–	IHM	1 mV MEP/0.2 Hz	40	T0 (*x*2)
Siebner et al. (2004/*x*2)	5 (*x*1) 8(*x*1)	10 min (*x*2)	A, C (*x*1)A, C, S (*x*1)	–/–	IHM	0.7–1 mV MEP/0.25 Hz	30	T0 (*x*2)
Nitsche et al. (2004/*x*2)	6 (*x*1) 12 (*x*1)	9 min C/13 min A (*x*2)	A, C (*x*2)	–/–	IHM	1 mV MEP/0.25 Hz	20 bl/15 @ 5 min	T0 – T60 (*x*2)
Nitsche et al. (2004)	10	9 min C/13 min A	A, C	–/–	IHM	1 mV MEP/0.25 Hz	20 bl/15 @ 5 min	T0 – T60
Nitsche et al. (2004)	12	9 min C/13 min A	A, C	–/–	IHM	1 mV MEP/0.25 Hz	20 bl/15 @ 5 min	T0-T60
Quartarone et al. (2005)	8	10 min	A, C, S	–/–	IHM	0.8–1 mV MEP/?	20	T0
Nitsche et al. (2006)	12	9 min C/13 min A	A, C	–/–	IHM	1 mV MEP/0.25 Hz	20 bl/15 @ 5 min	T0 – T60
Power et al. (2006)	10	10 min	A, C, S	–/–	IHM	0.8–1 mV MEP/?	15 @ 5 min	T0 – T10
Nitsche et al. (2007/*x*2)	12 (*x*2)	10 min (*x*2)	A, C (*x*2)	–/–	IHM	1 mV MEP/0.25 Hz	20 bl/15 @ 5 min	T0 – T60 (*x*2)
Kuo et al. (2007)	7	9 min C/13 min A	A, C	–/–	IHM	1 mV MEP/0.25 Hz	20 @ 5 min	T0 – T60
Antal et al. (2007)	12(*T5/30*) 6(*T60*)	10 min	A, C	–/–	IHM	1 mV MEP/0.25 Hz	50 bl/25 @ 5 min	T5 – T60
Kuo et al. (2008)	7	9 min Cathode/13 min Anode	A, C	–/–	IHM	?/?	20 @ 5 min	T0 – T60
Nitsche et al. (2009)	12	9 min C/13 min A	A, C	–/–	IHM	1 mV MEP/0.25 Hz	20 @ 5 min	T0 – T60
Monte-Silva et al. (2009/*x*4)	12 (*x*4)	9 min C/13 min A (x4)	A, C	–/–	IHM	1 mV MEP/0.25 Hz	25 @ 5 min	T0 – T60 (x4)
Bradnam et al. (2010)	15	15 min	C	–/–	INF	?/0.2 Hz	48 @ 20 min	T0, T20
Monte-Silva et al. (2010/*x*2)	12 (*x*2)	9 min (x1)18 min (x1)	C	–/–	IHM	1 mV MEP/0.25 Hz	25 @ 5 min	T0 – T60 (x2)
Bradnam et al. (2011)	18	15 min	C, S	–/–	IHM	?/0.2 Hz	16	T30
Fricke et al. (2011)	8 – A 9 – C	10 min	A, C	–/–	IHM	1 mV MEP/0.25 Hz	25 bl/continuous 1st 5 min/30 @ 5 min	T0 – T60
List et al. (2011)	12	10 min	C	–/–	IHM	0.5–1 mV MEP/0.1 Hz	20	T0
Munneke et al. (2011/*x*2)	10 (*x*2)	11 min (*x*1)15 min (*x*1)	C	–/–	IHM	0.5 mV MEP/0.25 Hz	30	T5, T20 (*x*2)
Scelzo et al. (2011)	12	13 min	A	–/–	IHM	110% rMT/0.125 Hz	5	T0
Thirugnanas-ambandam et al. (2011)	16	20 min	A, C	–/–	IHM	1 mV MEP/0.25 Hz	20	T0
Di Lazzaro et al. (2012)	30 (*T0*)	20 min	C	–/–	IHM	120% rMT/?	10	T0, T30

Table 1 (*continued*)

Paper/# of studies	*N*	tDCS duration	tDCS polarities	DB/NN	Tar.	TMS power/frequency	# of MEPs averaged	*T*(*x*)
	15 (*T30*)							
Hasan et al. (2012)	18	9 min	C	−/−	IHM	1 mV MEP/?	40	T5
Suzuki et al. (2012)	9	10 min	A, C, S	−/−	IHM	110% rMT/?	17	T0, T10, T30
Monte-Silva et al. (2013/*x*2)	15 (*x*2)	13 min (*x*1)26 min (*x*1)	A	Y*x*1/−	IHM	1 mV MEP/0.25 Hz	25 @ 5 min	T0−T60 (*x*2)
Hasan et al. (2013)	20	9 min	C	−/−	IHM	1 mV MEP/0.2 Hz	30	T1, T30
Batsikadze et al. (2013/*x*2)	9 (*x*1) 8 (*x*1)	20 min (*x*2)	C (*x*1)S (*x*1)	−/−	IHM	1 mV MEP/?	20	T0, T60 (*x*1)T0, T30, T60 (*x*1)
Schabrun et al. (2013/*x*3)	21 – A 9 – C 13 – S	20 min (*x*3)	A (*x*1)C (*x*1)S (*x*1)	−/−	IHM	1 mV MEP/?	48	T0, T10 (*x*3)
Simis et al. (2013)	11	20 min	A, S	Y/-	IHM	?	?	T0
Teo et al. (2014)	58	9 min	A	Y/-	IHM	120% rMT/?	24 bl/10 @ 5 min	T0−T60
High density (> 0.02857 mA/cm^2)/long duration (> 7 min) − tested muscle at rest								
Ardolino, Bossi et al. (2005)	7 – C 5 – S	10 min/0.04285 mA/cm^2	C, S	−/−	IHM	120% rMT/0.15 Hz	24	T0, T20, T60
Jeffery et al. (2007/*x*2)	8	10 min/0.0571 mA/cm^2	A, C, S	−/−	LM	1 mV MEP/?	20	T0, T10, T30, T60
Furubayashi et al. (2008)	8	10 min/0.0667 mA/cm^2	A, C	−/−	IHM	?/?	?	T0−T20
Jefferson et al. (2009/*x*3)	11 (*x*1) 13 (*x*2)	10–20 min/0.04–0.08 mA/cm^2	A, C (x3)S (x2)	Y/-	PM	Threshold +10% SO/?	10	T0, T15, T30, T60
Groppa et al. (2010)	10	10 min/0.0625 mA/cm^2	A, C	−/Y	IHM	0.75 mV MEP/0.25 Hz	30	T5, T10, T20
Roche et al. (2011)	5	20 min/0.05714 mA/cm^2	A	−/−	LM	120% rMT/0.25 Hz	20	T0
Kuo et al. (2013)	14	10 min/0.05714 mA/cm^2	A, C	−/−	IHM	1 mV MEP/?	20	T0−T60
Batsikadze et al. (2013)	14	20 min/0.05714 mA/cm^2	A, C	−/−	IHM	1 mV MEP/?	20	T0, T60
Galvez et al. (2013/*x*2)	11 (*x*2)	20 min/0.05714 mA/cm^2 (x2)	A	−/−	IHM	1 mV MEP/0.2 Hz	20	T0−60 (x2)
Tremblay et al. (2013)	10	20 min/0.06 mA/cm^2	A, C	−/Y	IHM	1 mV MEP/0.11 Hz	20	T0
Schmidt et al. (2013)	16	20 min/0.0438 mA/cm^2	C, S	Y/Y	IHM	1 mV MEP/?	20	T0
Pellicciari et al. (2013)	18	13 min/0.04 mA/cm^2	A, C	−/Y	IHM	110% rMT/0.25–0.5 Hz	100	T0, T30
Miyaguchi et al. (2013)	9	10 min/0.0571 mA/cm^2	C	−/−	IHM	1 mV MEP/0.2 Hz	12	T0, T10

General notes: DB=double-blind experimental design with regards to tDCS condition (not any included pharmacological arm); NN=neuronavigation system used to guide TMS; Tar.=target muscle tested; *T*(*x*)=time (in minutes) post-stimulation that measurements were reported and pooled for this analysis. A=anode; C=cathode; S=sham; IHM=intrinsic hand muscle (first dorsal interosseous; abductor digiti minimi; abductor pollicis brevis) LM=leg muscle (Tibialis Anterior; Vastus Lateralis); PM=pharyngeal muscle; INF=infraspinatus; BB=bicep brachii; ECR=extensor carpi radialis; SO=stimulator output; rMT=resting motor threshold; aMT=active motor threshold. TMS power refers to the TMS output utilized in each experiment. For example, 1 mV means the stimulator was set to a level which consistently evoked peak-to-peak MEP amplitudes of 1 mV.

Low intensity short-duration notes: two studies from Nitsche and Paulus (2000) and one study from Nitsche and Paulus (2001) were excluded due to no SD or SEM being discernable from reported data. One study from Fricke et al. (2011) was excluded due to SD over 100%. A sham condition from Quartarone et al. (2004) was excluded due to reporting MEP modulation during motor imagery only.

Low intensity long-duration notes: One study from Nitsche and Paulus (2001) was excluded due to no SD or SEM being discernable from reported data. Boros et al. (2008) and Cambieri et al. (2012) were excluded due to SD over 100%. McCambridge et al. (2011) was excluded due to no timing of post-stimulation MEP measurements being discernable from reported data. One study from Monte-Silva et al. (2009) was excluded due to it including data reported in a prior report. Two studies from Antal et al. (2007) were omitted due to including a cognitive and/or motor task during tDCS stimulation. Four studies from Miyaguci et al. (2013) were omitted due to including a passive or active motor activity during stimulation. One study from Bradnam et al. (2010) was omitted due to targeting a muscle under voluntary isometric contraction.

High intensity notes: one study from Jefferey et al. (2007) was excluded due to targeting a muscle under voluntary isometric contraction. Paquette et al. (2011) and Kim et al. (2013) were excluded due to SD over 100%.

single lab. Due to this inclusion criterion, a number of outcome measures extant in the literature were omitted due to only being reported by a single research group (see Table S1). We want to emphasize that this *does not* suggest said research is in any way faulty or incorrect; rather, that inter-group replication as necessary in order to eliminate any potential non-tDCS influential outcome factors,

Additional information for each measure is outlined below.

2.2. TMS: MEP amplitude

Papers included in this analysis were obtained from a PubMed database search (January 20, 2014). The search term "transcranial direct current stimulation" generated 1040 papers. Initially, the abstract of each paper was read to determine outcome measures. If a TMS measure was included, the methods section was read to determine what protocol/s were utilized.

The only absolute inclusion criteria for this measure were MEPS must have been obtained in healthy adults (18–50), the muscular representation of the tested muscle must have been covered with the active electrode (this excludes measure of ipsilateral muscular effect), the tested muscle must have been at rest (not voluntarily contracted) and the reported SD must have been below 100% (this final quality-assessment criterion was included to ensure excessively variable results did not inequitably influence pooling). Any study which fulfilled these criteria was included in analysis, including the control condition/s in any study exploring the interaction between active tDCS and a secondary drug or device. Included studies were grouped according to stimulation density, electrode montage, and stimulation duration (Table 1: see Supplementary material for complete MEP amplitude study selection flow-chart).

As there is a growing body of research which suggests cognitive and/or behavioral activities undertaken during tDCS can influence the effects of stimulation (for discussion: Horvath et al., 2014), it is worth noting all studies included in the MEP analysis asked participants to sit comfortably and relax during stimulation. In addition, 5 studies have explored the effect of high density tDCS on MEP amplitude in muscles under voluntary isometric contraction. Unfortunately, as two reported SDs above 100% (failed to meet inclusion criteria), one utilized a shoulder reference electrode location, and one utilized only anodal stimulation, we were unable to pool and analyze data from this work (see Supplementary material for study selection flow-chart). Finally, two studies have explored the effects of Hi-Definition tDCS on MEP Amplitude (Caparelli-Daquer et al., 2012; Kuo et al., 2013). As both of these came from the same research group (and utilized equipment significantly different from other included studies), we did not include these in the analysis.

As the effects of tDCS may differ following short- and long-duration tDCS protocols (outlined above), analyses for this measure were initially divided into two groups: short-duration stimulation (1–7 min), and long-duration stimulation (>7 min). Additionally, several studies included in this section utilized a very-short duration stimulation protocol (4 s). As it is uncertain how these protocols affect outcome measures, we decide to analyze these studies separately (very-short duration: <1 min).

Finally, to determine if technological and methodological improvements have impacted the modulation effects of tDCS since 2000, we undertook a secondary analysis by dividing papers which explore the impact of low-density tDCS MEP amplitude into three temporal cohorts (*Cohort A:* 2000–2004; *Cohort B:* 2005–2009; *Cohort C:* 2010-Present) and comparing each. This was only possible for this outcome measure as there were not enough papers to undertake this analysis for any other outcome measure.

2.3. TMS: additional measures

See TMS method (above) for literature search and absolute inclusion criteria. Any study which fulfilled these criteria was included in analysis, including the control condition/s in any study exploring the interaction between active tDCS and a secondary drug or device. Included studies were grouped according to TMS outcome measure, stimulation density, electrode montage, and stimulation duration. Due to a lack of comparable studies, both low- and high-density stimulation intensities were included in a singular measure for cSP (Table 10: see Supplementary material for complete Additional TMS Measures study selection flow-chart). In addition, whereas two studies have explored additional TMS measures in muscles under voluntary isometric contraction (Jefferson et al., 2009; Kidgell et al. 2013a), one did not include numerical data; accordingly, we were unable to pool these papers. As all the studies that met our inclusion criteria targeted intrinsic hand muscles, we did not include this as a column in the relevant table below. Finally, again, it is worth noting all studies included in this section asked participants to sit comfortably and relax during tDCS (no cognitive or behavioral activities were undertaken during stimulation).

2.4. Event related potentials (ERPs)

See TMS method (above) for literature search and absolute inclusion criteria. Any study which fulfilled these criteria was included in analysis, including the control condition/s in any study exploring the interaction between active tDCS and a secondary drug or device. Included studies were grouped according to ERP component and, when possible, stimulation density, electrode montage, and stimulation duration. Due to a lack of comparable studies, varied density and/or varied electrode montages were pooled for several ERP measures (Table 14: see Supplementary material for complete ERP study selection flow-chart). With the exception of one study (Accornero et al., 2007), all studies included in this section asked participants to sit comfortably and relax during tDCS (no cognitive or behavioral activities were undertaken during stimulation). In Accornero et al. (2007), visual evoked potentials were elicited and measured during stimulation.

2.5. EEG power spectrum

See TMS method (above) for literature search and absolute inclusion criteria. Any study which fulfilled these criteria was included in analysis, including the control condition/s in any study exploring the interaction between active tDCS and a secondary drug or device. Included studies were grouped according to accompanying behavioral activity and, when possible, electrode montage and stimulation duration. Due to a lack of comparable studies, both low- and high-density stimulation intensities were included for each EEG power spectrum measure (Table 19: see Supplementary material for complete EEG power spectrum study selection flow-chart). As the majority of included studies simply provide a written description of any significant (or non-significant) differences without accompanying numerical data, we were unable to complete a mathematical analysis for any included measure. Instead, we have undertaken a qualitative comparison of relevant studies to ascertain if an effect has reliably been found. As above, with the exception of one study (Wirth et al., 2011), all studies included in this section asked participants to sit comfortably and relax during tDCS (no cognitive or behavioral activities were undertaken during stimulation). In Wirth et al. (2011), a semantic-interference task was undertaken during stimulation.

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2.6. Functional magnetic resonance imaging (fMRI)

See TMS method (above) for literature search and absolute inclusion criteria. Any study which fulfilled these criteria was included in analysis, including the control condition/s in any study exploring the interaction between active tDCS and a secondary drug or device. Included studies were grouped according to electrode location, neural region of interest (ROI) analysis reported, and, when possible, stimulation duration. Due to a lack of comparable studies, both low- and high-density stimulation intensities were included for each fMRI measure (Table 21: see Supplementary material for complete fMRI study selection flow-chart). As the majority of studies do not include discernable baseline measure values, it would be misleading to pool much of this data. In addition, as the included studies range from 2001 to 2013, the type of data reported is quite variable (as later studies utilize more modern methods of analysis than earlier studies). Accordingly, we have undertaken a qualitative comparison of relevant studies to ascertain if an effect has reliably been found. With the exception of three studies (Antal et al., 2011; Kwon and Jang, 2011; Saiote et al., 2013), all studies included in this section performed tDCS outside the fMRI and asked participants to sit comfortably/relax during tDCS (no cognitive or behavioral activities were undertaken during stimulation). In Antal et al. (2011), tDCS was delivered inside the scanner whilst the participants were at rest. In Kwon and Jang (2011), tDCS was delivered inside the scanner whilst the participants undertook a timed grasp/release motor activity during stimulation. Similarly, in Saiote et al. (2013) tDCS was delivered inside the scanner whilst the participants undertook a visuomotor learning task during stimulation.

3. Results

3.1. TMS: MEP Amplitude

3.1.1. Low-density: primary analysis.

3.1.1.1. Very-short duration stimulation (< 5 s). MEPs were measured in isolation (baseline) and immediately following short bursts of tDCS. Modulation was determined via normalizing MEP

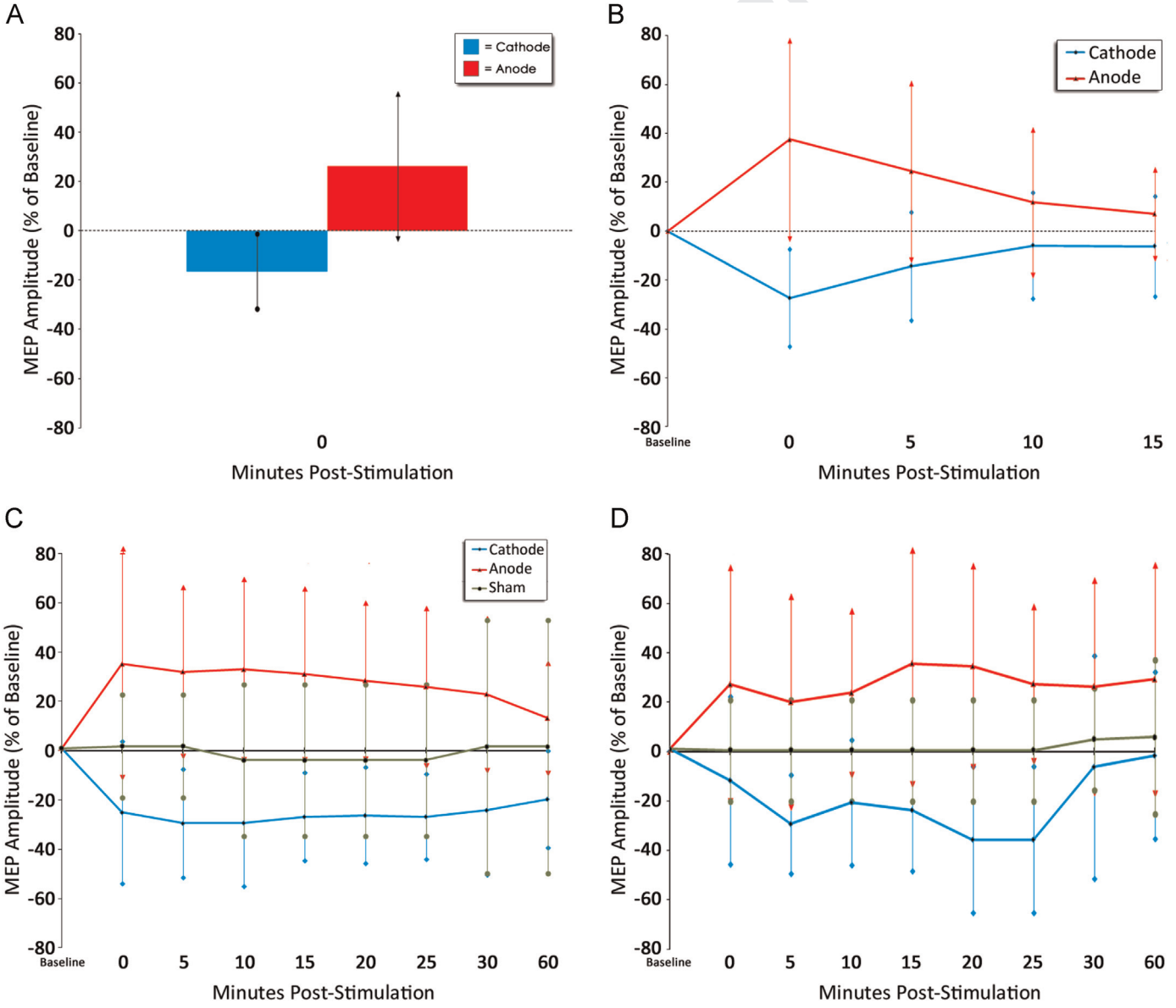

Fig. 1. Effects of tDCS on MEP amplitude (results pooled across all studies). (A) Low-density, very-short-duration (< 1 min) tDCS; (B) low-density, short duration (1–7 min) tDCS; (C) low-density, long duration (> 7 min) tDCS; (D) high-density, long-duration tDCS. Error bars: ± 1 SD.

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Table 2
Numerical values for low-density, very-short duration tDCS on MEP amplitude.

		N	Mean (% of baseline)	SD	95% u confidence interval
Low density (0.02857 mA/cm²)/very-short duration (< 1 min) – muscle at rest					
T0**	Cathode	76	−16.34	15.26	−19.771 < u < −12.909
	Anode	76	26.45	30.70	19.548 < u < 33.352
	Sham	–	–	–	–

[a]Difference between either stimulation condition and sham.
[b] Difference between stimulation conditions.

amplitude following stimulation to baseline levels. 5 papers comprising 7 studies utilized this paradigm and were pooled (Table 1). No studies utilized a control (sham) condition. Results suggest that cathodal stimulation diminishes and anodal stimulation increases MEP amplitude approximately 16% and 26%, respectively (Fig. 1a). An unpaired student's *t*-test ($t(150)=10.88$, $p<0.001$) showed this difference to be significant. (Table 2).

3.1.1.2. Short-duration stimulation (1–7 min). MEPs were measured pre-stimulation and continuously for 5–20 min post-stimulation. We pooled data at 5 min increments up to 15 min post-stimulation. 13 papers comprising 19 studies utilized this paradigm and were pooled (Table 1). No studies utilized a control (sham) condition. Results suggest that cathodal stimulation diminishes and anodal stimulation increases MEP amplitude immediately following stimulation approximately 27% and 38%, respectively (Fig. 1b). At T0, an unpaired student's *t*-test revealed a significant difference between stimulation conditions ($t(321)=18.147$, $p<0.001$). Significant differences occurred between stimulation conditions at all time points post-stimulation (Table 3).

3.1.1.3. Long-duration stimulation (> 7 min). MEPs were measured pre-stimulation and in blocks every 5 min post-stimulation. For our analysis, we pooled data at 5 min increments up to 30 min post-stimulation and at 60 min post-stimulation. 35 papers comprising 50 studies utilized this paradigm and were pooled (Table 1). 8 studies utilized a control (sham) condition – however, due to varying protocols, pooled sham data could only be obtained immediately, 10- and 30 min post stimulation. Results suggest that cathodal stimulation diminishes and anodal stimulation increased MEP amplitude immediately following stimulation approximately 26% and 35%, respectively (Fig. 1c). A one-way ANOVA (including sham) at T0 revealed a significant difference between conditions ($F(2, 873)=253.78$, $p<0.001$). Post-hoc tests revealed a significant difference between cathode and anode ($t(810)=21.93$, $p<0.001$), between cathode and sham ($t(462)=7.16$, $p<0.001$), and between anode and sham ($t(474)=5.58$, $p<0.001$).Significant differences occurred between stimulation conditions at all time points post-stimulation and between stimulation conditions and sham at T10 and T30 (Table 3 and 4).

Table 3
Numerical values for low-density, short duration tDCS on MEP amplitude.

		N	Mean (% of baseline)	SD	95% u confidence interval
Low density (0.02857 mA/cm²)/short duration (1–7 min) – muscle at rest					
T0**	Cathode	173	−27.29	19.93	−30.260 < u < −24.320
	Anode	150	37.54	41.84	30.844 < u < 44.236
	Sham	–	–	–	–
T5**	Cathode	152	−14.20	22.14	−17.720 < u < −10.680
	Anode	141	24.54	37.37	18.372 < u < 30.708
	Sham	–	–	–	–
T10**	Cathode	173	−5.84	21.62	−9.062 < u < −2.618
	Anode	158	11.92	31.01	7.085 < u < 16.755
	Sham	–	–	–	–
T15**	Cathode	103	−6.18	20.57	−10.153 < u < −2.207
	Anode	102	7.10	19.36	3.343 < u < 10.857
	Sham	–	–	–	–

[a]Difference between either stimulation condition and sham.
[b] Difference between stimulation conditions.

Table 4
Numerical values for low-density, long duration tDCS on MEP amplitude.

		N	Mean (% of baseline)	SD	95% u confidence interval
Low density (0.02857 mA/cm²)/long duration (> 7 min) – muscle at rest					
T0*	Cathode	400	−25.05	28.82	−27.883 < u < −22.217
	Anode	412	35.08	46.92	30.549 < u < 39.611
	Sham	64	1.81	20.82	−3.291 < u < 6.911
T5**	Cathode	287	−29.44	21.98	−31.983 < u < −26.897
	Anode	320	32.01	35.42	28.129 < u < 35.891
	Sham	–	–	–	–
T10*	Cathode	284	−29.26	25.81	−32.262 < u < −26.258
	Anode	341	32.88	37.78	28.870 < u < 36.890
	Sham	32	−3.88	30.82	−14.559 < u < 6.799
T15**	Cathode	227	−26.79	17.85	−29.112 < u < −24.468
	Anode	290	30.99	35.86	26.863 < u < 35.117
	Sham	–	–	–	–
T20**	Cathode	262	−26.24	19.51	−28.613 < u < −23.867
	Anode	290	28.40	32.76	24.629 < u < 32.171
	Sham	–	–	–	–
T25**	Cathode	227	−26.75	17.38	−29.011 < u < −24.489
	Anode	290	25.88	33.13	22.067 < u < 29.693
	Sham	–	–	–	–
T30*	Cathode	289	−24.14	26.10	−27.149 < u < −21.131
	Anode	299	22.87	32.10	19.231 < u < 26.509
	Sham	35	1.6	51.40	−15.429 < u < 18.629
T60**	Cathode	220	−19.68	19.71	−22.285 < u < −17.075
	Anode	274	13.15	23.48	10.370 < u < 15.930
	Sham	–	–	–	–

[a] Difference between either stimulation condition and sham.
[b] Difference between stimulation conditions.

3.1.2. High-density

3.1.2.1. Long-duration stimulation (> 7 min) – tested muscle at rest. MEPs were measured pre-stimulation and in blocks every 5 min post-stimulation. For our analysis, we pooled data at 5 min increments up to 30 min post-stimulation and at 60 min post-stimulation. 13 papers comprising 16 studies utilized this paradigm and were pooled (Table 1). 5 studies utilized a control (sham) condition – however, due to varying protocols, pooled sham data could only be obtained immediately post stimulation, at T30, and at T60. Results suggest that cathodal stimulation diminishes and anodal stimulation increased MEP amplitude immediately following stimulation approximately 22% and 30%, respectively (Fig. 1d). A one-way ANOVA (including sham) at T0 revealed a significant difference between conditions ($F(2, 324)=33.228$, $p<0.001$). Post-hoc tests revealed a significant difference between cathode and anode ($t(272)=7.621$, $p<0.001$), between cathode and sham ($t(183)=2.438$, $p=0.016$), and between anode and sham ($t(193)=3.868$, $p<0.001$).. Significant differences occurred between stimulation conditions at all measurable time points (Table 5). Interestingly, corrected *t*-tests at T30 and T60 reveal that, although anode differs from sham at both these time points (T30: $t(174)=4.797$, $p<0.001$; T60: $t(125)=2.590$, $p=0.011$), cathode does not (T30: $t(107)=1.344$, $p=0.181$; T60: $t(123)=1.102$, $p=-0.273$).

3.1.3. Low-density: secondary analysis (temporal cohorts).

3.1.3.1. Very-short duration stimulation (< 1 min). As the last time this measure was reported in the literature was 2007, only *Cohorts A and B* could be compared. An unpaired student's *t*-test revealed

Table 5
Numerical values for high-density, long duration tDCS on MEP amplitude.

		N	Mean (% of baseline)	SD	95% *u* confidence interval
High density (> 0.02857 mA/cm²)/long duration (> 7 min) – muscle at rest					
T0*	Cathode	132	−11.66	33.87	−17.491 < *u* < −5.828
	Anode	142	27.13	48.51	19.083 < *u* < 35.178
	Sham	53	0.49	20.36	−5.121 < *u* < 6.101
T5**	Cathode	32	−29.25	19.83	−36.121 < *u* < −22.379
	Anode	54	20.04	43.97	12.885 < *u* < 32.195
	Sham	–	–	–	–
T10**	Cathode	40	−20.55	25.38	−28.667 < *u* < −12.433
	Anode	71	23.72	34.52	15.549 < *u* < 31.891
	Sham	–	–	–	–
T15**	Cathode	48	−23.64	24.62	−30.789 < *u* < −16.491
	Anode	70	35.54	49.93	23.635 < *u* < 47.445
	Sham	–	–	–	–
T20**	Cathode	39	−35.60	29.57	−44.881 < *u* < −26.319
	Anode	54	34.37	42.17	23.122 < *u* < 45.618
	Sham	–	–	–	–
T25	Cathode	–	–	–	–
	Anode	36	27.33	32.55	32.5531
	Sham	–	–	–	–
T30*	Cathode	77	−6.20	45.00	−16.414 < *u* < 4.014
	Anode	99	26.27	44.20	17.454 < *u* < 35.086
	Sham	32	4.97	20.63	−2.468 < *u* < 12.408
T60*	Cathode	93	−1.65	33.64	−8.578 < *u* < 5.278
	Anode	95	29.17	47.65	19.463 < *u* < 38.877
	Sham	32	5.81	31.13	−5.414 < *u* < 17.034

[a] Difference between either stimulation condition and sham.
[b] Difference between stimulation conditions.

no significant difference in reported cathodal effects ($t(74)=1.490$, $p=0.140$). However, an unpaired student's *t*-test revealed a significant difference in reported anodal effects ($t(74)=5.265$, $p<0.001$) such that the effects are significantly smaller in more recent studies (Table 6; Fig. 2b).

3.1.3.2. Short-duration stimulation (1–7 min). One-way ANOVAs were conducted at each time point pooled post-stimulation (Table 7). Of note, recent studies (*Cohort C*) showed significantly smaller effects immediately following anodal stimulation compared to earlier studies (Fig. 2c,d).

3.1.3.3. Long-duration stimulation (> 7 min). One-way ANOVAs were conducted at each time point pooled post-stimulation (Table 8). Of note, recent studies (*Cohort C*) showed significantly smaller effects immediately following cathodal stimulation compared to earlier studies (*Cohort A*). In addition, *Cohort C* showed significantly smaller effects at *every* time point post-anodal stimulation compared to *Cohorts A and B* (Fig. 2e and f).

3.2. TMS: additional measures

3.2.1. Resting and active motor threshold (rMT and aMT) intensity

rMTs were measured prior to and immediately following stimulation only. 6 studies have explored the impact of tDCS on this measure and were pooled for rMT analysis (Table 9). 1 study utilized a control (sham) condition. A one-way ANOVA revealed no significant difference between conditions ($F(2, 115)=0.056$, $p=0.946$: Table 11; Fig. 3a). Table 10). An additional 8 studies which have explored the impact on this measure reported no effect – although none supplied numerical data (see Table 10 notes).

aMTs were measured prior to and immediately following stimulation only. 5 studies have explored the impact of tDCS on this measure and were pooled for aMT analysis (Table 9). A one-way ANOVA revealed no significant difference between conditions ($F(2, 117)=0.585$, $p=0.559$: Table 10; Fig. 3b).

4 studies from 3 papers have explored the effects of very-short duration (< 5 sec) and short-duration (1–7 min) stimulation on rMT (Cengiz et al., 2013; Mordillo–Mateos et al., 2012; Nitsche et al., 2005). Although each reported no effect of tDCS on rMT, due to varying protocols, no data could be pooled.

3.2.2. Cortical silent period (cSP) duration

cSPs were measured prior to and immediately following stimulation only. 7 studies have explored the impact of tDCS on this measure. Each reported no effect of tDCS on cSP. However, only 3 of these studies reported numerical data and could be pooled (Table 9). One study utilized a control (sham) condition. A one-way ANOVA revealed no significant difference between conditions ($F(2, 53)=0.751$, $p=0.477$: Table 11; Fig. 3c).

3.2.3. Short interval cortical inhibition (SICI) and intracortical facilitation (ICF) duration

For this analysis, we combined all ISIs thought to lead to SICI (2, 3, 4, and 5 ms) into a single measure and all ISIs thought to lead to ICF (7, 9, 10, 12,and 15ms) into a single measure. So as not to compound N, weighted averages and pooled standard deviations were determined for any paper that explored more than one of these ISIs. In addition, a post-stimulation MEP amplitude comparison was made between groups.

SICI and ICF were typically measured prior to and immediately following stimulation only. 8 studies have explored the impact of tDCS on these measures and were pooled for analysis (Table 9). Two studies utilized a control (sham) condition. With regards to SICI, student's *t*-tests (Cathode: $t(172)=0.076$, $p=0.940$; Anode: $t(82)=1.616$, $p=0.110$; Sham: $t(30)=0.426$, $p=0.673$; Fig. 3d) did not reveal a significant difference between pre- and post-scores for any condition (Table 12). A one-way ANOVA between post-stimulation scores did reveal a significant difference ($F(2, 122)=9.717$, $p<0.001$). Post-hoc bonferroni correct *t*-tests revealed no difference between cathode and sham ($t(81)=1.477$, $p=0.144$) or anode and sham ($t(56)=1.420$, $p=0.1611$), but a significant difference between anode and cathode ($t(107)=4.931$, $p<0.001$).

Table 6
Temporal analysis numerical values for low-density, very-short duration tDCS on MEP amplitude.

			N	Mean (% of baseline)	SD	95% *u* confidence interval
Low density (0.02857 mA/cm²)/very-short duration (< 1 min) – muscle at rest						
Cathode	**T0**	2000–2004	40	−18.85	6.95	−21.004 < *u* < −16.696
		2005–2009	36	−13.67	20.75	−20.448 < *u* < −6.892
		2010-Present	–	–	–	–
Anode	**T0***	2000–2004	40	41.55	32.40	31.509 < *u* < 51.591
		2005 – 2009	36	9.67	17.30	4.019 < *u* < 15.321
		2010-Present	–	–	–	–

[a] Difference between temporal cohorts.

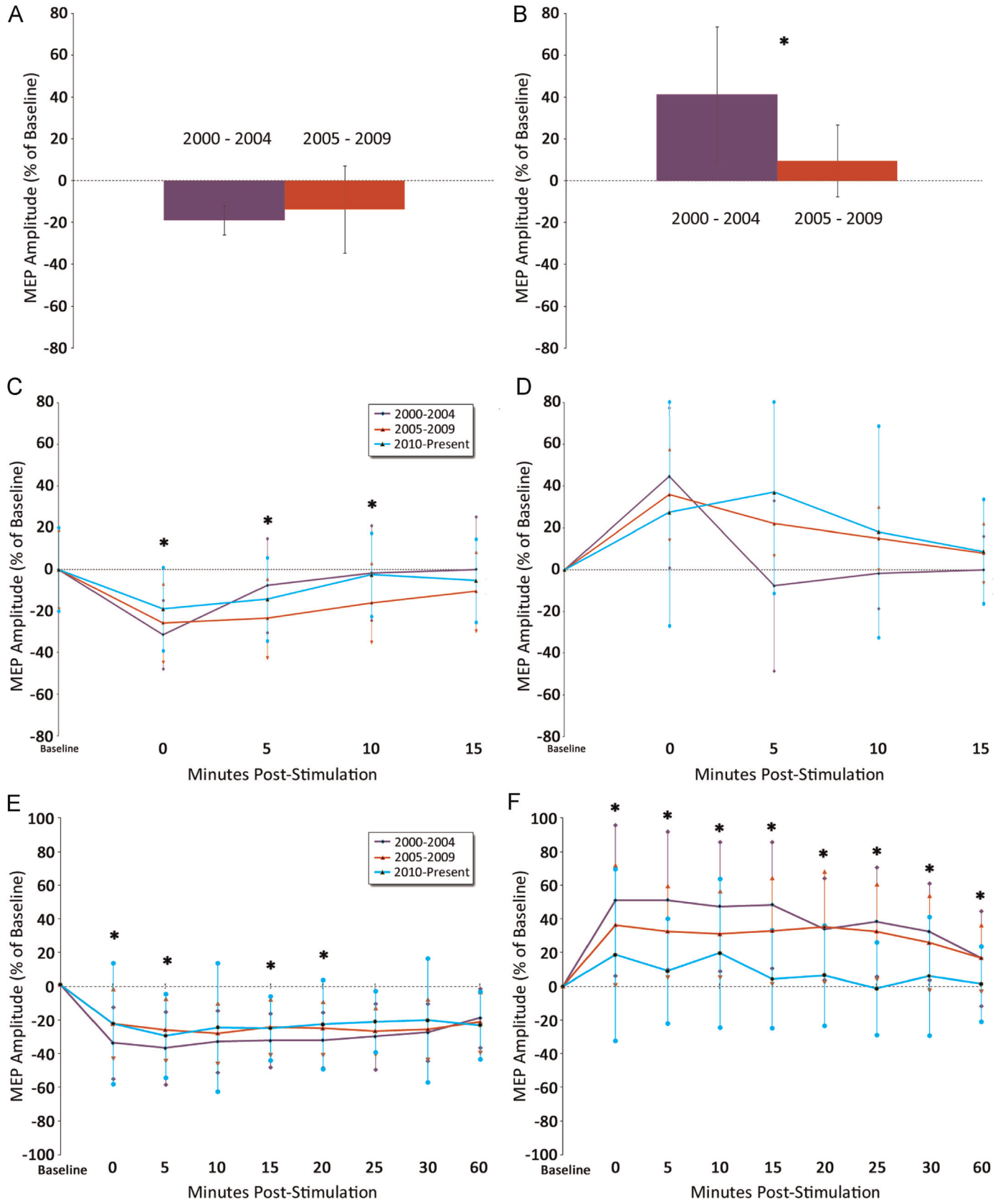

Fig. 2. Effects of tDCS on MEP amplitude (results pooled according to temporal cohorts). (A and B) Low-density, very-short-duration (< 1 min) cathodal and anodal tDCS, respectively; (C and D) low-density, short duration (1–7 min) cathodal and anodal tDCS, respectively; (E and F) low-density, long duration (> 7 min) cathodal and anodal tDCS, respectively. Error bars: ± 1 SD.

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Table 7
Temporal analysis numerical values for low-density, short duration tDCS on MEP amplitude.

			N	Mean (% of baseline)	SD	95% *u* confidence interval
Low density (0.02857 mA/cm²)/short duration (1–7 min) – muscle at rest						
Cathode	**T0**	2000–2004	90	−31.34	16.57	$-34.763 < u < -27.917$
		2005–2009	48	−25.75	11.63	$-29.040 < u < -22.460$
		2010-Present	26	−16.54	29.83	$-28.591 < u < -4.489$
	T5*	2000–2004	69	−7.71	22.56	$-13.033 < u < -2.387$
		2005–2009	48	−23.50	12.17	$-27.093 < u < -19.907$
		2010-Present	26	−8.54	31.07	$-21.092 < u < 4.012$
	T10*	2000–2004	90	−1.72	22.80	$-6.431 < u < 2.991$
		2005–2009	48	−16.00	13.44	$-19.802 < u < -12.198$
		2010-Present	26	−2.62	26.03	$-13.136 < u < 7.896$
	T15	2000–2004	30	0.00	25.25	$-9.036 < u < 9.036$
		2005–2009	48	−10.5	14.53	$-14.611 < u < -6.389$
		2010-Present	16	−6	28.71	$-21.288 < u < 9.288$
Anode	**T0***	2000–2004	64	44.67	43.73	$33.956 < u < 55.384$
		2005–2009	48	36.00	22.75	$29.564 < u < 42.436$
		2010-Present	46	25.61	26.65	$17.909 < u < 33.311$
	T5	2000–2004	57	18.74	40.88	$8.127 < u < 29.353$
		2005–2009	48	22.00	16.18	$17.423 < u < 26.577$
		2010-Present	36	19.11	30.90	$9.016 < u < 29.204$
	T10*	2000–2004	64	5.09	16.89	$0.952 < u < 9.228$
		2005–2009	48	15.00	16.11	$10.442 < u < 19.558$
		2010-Present	38	15.95	39.81	$3.292 < u < 28.608$
	T15	2000–2004	18	1.33	16.04	$-6.647 < u < 9.307$
		2005–2009	48	8.00	15.21	$3.369 < u < 12.303$
		2010-Present	28	9.86	27.46	$-0.830 < u < 20.550$

[a] Difference between temporal cohorts.

With regards to ICF, student's *t*-tests (Cathode: $t(132)=0.549$, $p=0.584$; Anode: $t(82)=0.799$, $p=0.427$; Sham: $t(24)=1.235$, $p=0.229$; Fig. 3e) did not reveal a significant difference between pre- and post-scores for any condition (Table 12). A one-way ANOVA between post-stimulation scores only did not reveal a significant difference between groups ($F(2,122)=1.700$, $p=0.187$).

3 studies have examined the effect of very-short duration (<5 s) and short-duration (1–7 min) stimulation on SICI and ICF ((Fricke et al., 2011; Munneke et al., 2011; Nitsche et al., 2005). However, as one of these studies reported SDs far above 100% and the remaining two came from the same research group, we did not pool this data for analysis.

3.3. Event related potentials (ERPs)

3.3.1. P100 visual evoked potential (VEP) amplitude: low and high contrast stimuli

P100 amplitudes were typically measured pre-stimulation and in blocks every 10 min post-stimulation (up to 30 min). 3 Studies met criteria for inclusion in the P100 analysis (Table 13). No studies utilized a sham control condition. With regards to low-contrast stimuli, student's *t*-tests revealed no significant difference between stimulation conditions at any time point (T0: $t(50)=1.472$, $p=0.147$; T10: $t(50)=1.768$, $p=0.084$; T20: $t(50)=0.779$, $p=0.440$; T30: $t(50)=0.492$, $p=0.625$; Fig. 4a; Table 14). With regards to high contrast stimulation, student's *t*-tests revealed no significant difference between stimulation conditions at any time point (T0: $t(61)=0.931$, $p=0.356$; T10: $t(50)=0.816$, $p=0.419$; T20: $t(50)=0.080$, $p=0.937$; T30: $t(50)=0.837$, $p=0.406$; Fig. 4b; Table 14) In addition, all included studies reported no effect of tDCS on the latency of the P100 component; although no discernable numerical data was available for pooling.

3.3.2. N20 somatosensory evoked potential (SEP): median nerve electrical stimuli

N20 amplitudes were measured pre-, immediately, 15 min, and 20 min post-stimulation. Due to constraints in the sham condition, time points T15 and T20 were combined into a single measure for each group (whilst maintaining *N*). 3 Studies met criteria for inclusion in this analysis (Table 13). One study utilized a control (sham) condition. A student's *t*-tests at T0 revealed no significant difference between stimulation conditions (T0: $F(2, 67)=1.895$, $p=0.158$; T20: $F(2)=1.220$, $p=0.302$). This non-significance continued at each time point post-stimulation (Table 15; Fig. 4c). In addition, all included studies reported no effect of tDCS on the N30 SEP component; though, no discernable numerical data was available for pooling.

3.3.3. N2 and P2 laser evoked potential (LEP): heat pain stimuli

N2 and P2 amplitudes were measured prior to and immediately following stimulation only. 3 Studies met criteria for inclusion in this analysis (Table 13). One-way ANOVAs revealed no significant difference between groups for either outcome measure (N2: $F(2, 76)=0.625$, $p=0.538$; P2: $F(2, 76)=0.997$, $p=0.374$; Table 16; Fig. 4d and e). In addition, all included studies noted no effect of tDCS on the amplitude of the N1 LEP component or any componential latency; although not enough data was available for pooling. Finally, (Terney et al., 2008) and (Csifcsak et al., 2009) further noted no effect of tDCS on LEP threshold; though, again, no discernable numerical data was available for pooling.

3.3.4. Mu/Alpha event related desynchronization (ERD): motor imagery

Mu/Alpha ERD percentage was measured prior to and immediately following stimulation only. 3 studies met criteria for inclusion in this analysis (Table 13). A one-way ANOVA revealed no significant difference between groups ($F(2, 94)=0.420$, $p=0.658$; Table 17; Fig. 4f).

3.4. EEG power spectrum results

3.4.1. Oscillation frequency power: at rest

4 studies have explored the effect of tDCS on resting state EEG oscillatory power using comparable protocols (Table 18). With

Table 8
Temporal analysis numerical values for low-density, long duration tDCS on MEP amplitude.

			N	Mean (% of baseline)	SD	95% *u* confidence interval
Low density (0.02857 mA/cm^2)/long duration (> 7 min) – muscle at rest						
Cathode	**T0***	2000–2004	108	−33.60	21.37	$-37.630 < u < -29.570$
		2005–2009	128	−22.25	22.12	$-26.082 < u < -18.418$
		2010-Present	164	−−22.13	35.90	$-27.665 < u < -16.595$
	T5*	2000–2004	72	−36.64	21.54	$-41.615 < u < -31.665$
		2005–2009	132	−25.87	19.92	$-29.268 < u < -22.472$
		2010-Present	71	−29.35	24.76	$-35.109 < u < -23.591$
	T10	2000–2004	72	−32.75	18.25	$-36.996 < u < -28.534$
		2005–2009	132	−27.89	19.41	$-31.201 < u < -24.579$
		2010-Present	62	−24.35	37.98	$-33.804 < u < -14.896$
	T15*	2000–2004	72	−32.19	15.96	$-35.877 < u < -28.503$
		2005–2009	122	−24.14	18.02	$-27.338 < u < -20.942$
		2010-Present	33	−24.82	19.00	$-31.303 < u < -18.337$
	T20*	2000–2004	72	−31.92	16.44	$-35.717 < u < -28.123$
		2005–2009	122	−24.90	17.38	$-27.984 < u < -21.816$
		2010-Present	68	−22.60	26.50	$-29.014 < u < -16.186$
	T25	2000–2004	72	−29.75	19.63	$-34.284 < u < -25.216$
		2005–2009	122	−26.54	15.36	$-29.266 < u < -23.814$
		2010-Present	33	−21.00	18.23	$-27.220 < u < -14.780$
	T30	2000–2004	72	−27.39	16.96	$-31.308 < u < -23.472$
		2005–2009	122	−25.48	19.42	$-28.926 < u < -22.034$
		2010-Present	95	−20.18	36.83	$-27.586 < u < -12.774$
	T60	2000–2004	102	−18.82	17.63	$-22.241 < u < -15.399$
		2005–2009	125	−21.15	19.63	$-24.591 < u < -17.709$
		2010-Present	42	−23.07	20.02	$-29.125 < u < -17.015$
Anode	**T0***	2000–2004	123	50.87	44.78	$42.956 < u < 58.784$
		2005–2009	128	36.38	37.20	$29.935 < u < 42.825$
		2010-Present	176	18.65	50.94	$11.124 < u < 26.176$
	T5*	2000–2004	87	51.09	41.07	$42.260 < u < 59.720$
		2005–2009	132	32.58	28.64	$27.694 < u < 37.466$
		2010-Present	96	9.019	31.05	$2.808 < u < 15.230$
	T10*	2000–2004	87	47.33	38.53	$39.234 < u < 55.426$
		2005–2009	132	30.95	27.07	$26.332 < u < 35.568$
		2010-Present	137	19.70	44.14	$12.309 < u < 27.091$
	T15*	2000–2004	87	48.31	37.61	$40.407 < u < 56.213$
		2005–2009	122	32.88	32.91	$27.040 < u < 38.720$
		2010-Present	96	4.29	28.94	$-1.499 < u < 10.079$
	T20*	2000–2004	87	34.01	30.25	$27.653 < u < 40.367$
		2005–2009	122	35.32	34.35	$29.225 < u < 41.415$
		2010-Present	96	6.47	29.70	$0.529 < u < 12.411$
	T25*	2000–2004	87	38.39	32.41	$31.580 < u < 45.200$
		2005–2009	122	32.57	29.64	$27.310 < u < 37.830$
		2010-Present	96	−1.30	27.36	$-6.733 < u < 4.173$
	T30*	2000–2004	87	32.34	28.66	$26.318 < u < 38.362$
		2005–2009	122	25.78	29.53	$20.540 < u < 31.020$
		2010-Present	105	6.08	35.17	$-0.647 < u < 12.807$
	T60*	2000–2004	77	16.55	28.05	$10.285 < u < 22.815$
		2005–2009	116	16.79	21.09	$12.952 < u < 20.628$
		2010-Present	96	1.48	22.25	$-2.971 < u < 5.931$

[a] Difference between temporal cohorts.

regards to cathodal stimulation, (Ardolino et al., 2005) reported a significant increase in the power of delta oscillations (compared to sham), (Pellicciari et al., 2013) reported an increase in the power of alpha and theta oscillations following cathodal stimulation (although this increase was comparable to increases following anodal stimulation and no sham condition was used), (Notturno et al., 2013) reported a significant decrease in power of alpha oscillations (compared to sham), and (Matsumoto et al., 2010) reported no effect on any oscillatory frequency (compared to sham). Each paper reported no significant effect of cathodal stimulation on any other oscillatory frequency (Table 19).

With regards to anodal stimulation, (Pellicciari et al., 2013) reported an increase in the power of alpha and theta frequencies (although this increase was comparable to increases following cathodal stimulation and no sham condition was used), whilst (Matsumoto et al., 2010) and (Notturno et al., 2013) both reported no effect of anodal stimulation on any oscillatory frequency (compared to sham: Table 19).

3.4.2. Oscillation frequency power (and P300 ERP): during N-Back working memory task

2 Studies have explored the effect of tDCS on EEG oscillatory power and P300 ERP characteristics during an N-Back task using comparable protocols (Table 18); unfortunately, as one of these studies only explored anodal stimulation, we will be unable to discuss the effects of cathodal stimulation. (Keeser et al., 2011) reported a reduction of absolute Delta power across frontal electrodes during a 2-back task (but not during a 0- or 1-back task: compared to sham). These researchers did not find any effect of tDCS on the theta, alpha, beta, or gamma bands (for 10 min following stimulation) during any N-Back condition. In addition, this group reported no significant change in P300 amplitude or latency at Pz (although they reported some attenuation at other electrodes, Pz was the only electrode explored in the second included study). Zaehle et al. (2011) reported no significant differences in frequency power following anodal stimulation (compared to sham). In addition, these researchers reported no significant difference in P300 amplitude or latency at Pz (Table 19).

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Table 9
Studies exploring the effects of long duration (> 7 min) tDCS on TMS measured resting motor threshold levels, active motor threshold levels, cortical silent period, short interval cortical inhibition, and intracortical facilitation.

Paper/# of studies	*N*	tDCS duration	tDCS polarities	DB/NN	Parameters	#Averaged
Resting motor threshold						
Lang et al. (2004)	5	10 min	A, C	–/–	5 of 10 MEPs between 50–100 uV	–
Quartarone et al. (2005)	8	10 min	A, C, S	–/–	5 of 10 MEPs above 50 uV	–
Nitsche et al. (2005)	12	9 min C/11 min A	A, C	–/–	3 of 6 MEPs above 50 uV	–
Scelzo et al. (2011)	12	13 min	A	–/–	5 of 10 MEPs above 50 uV	–
Hasan et al. (2012)	18	9 min	C	–/–	5 of 10 MEPs above 50 uV	–
Di Lazzaro et al. (2012)	30	20 min	C	–/–	5 of 10 MEPs above 50 uV	–
Active motor threshold						
Lang et al. (2004)	5	10 min	A, C	–/–	5 of 10 MEPs between 200–300 uV (contraction)	–
Quartarone et al. (2005)	8	10 min	A, C, S	–/–	5 of 10 MEPs above 200 uV (contraction)	–
Nitsche et al. (2005)	12	9 min C/11 min A	A, C	–/–	3 of 6 MEPs greater than background activity (15% contraction)	–
Thirugnanas-ambandam et al. (2011)	16	20 min	A, C	–/–	5 of 10 MEPs above 100 uV (peak-to-peak: 15% contraction)	–
Di Lazzaro et al. (2012)	30	20 min	C	–/–	5 of 10 MEPs above 200 uV (20% contraction)	–
Cortical silent period (cSP)						
Hasan et al. (2012)	18	9 min *0.258 mA/cm²*	C	–/–	1 mV MEP w/25–30% contraction	10*?*
Suzuki et al. (2012)	6	10 min*0.258 mA/cm²*	A, C, S	–/–	110% rMT w/10–20% contraction	10*Rel cSP*
Tremblay et al. (2013)	10	20 min *0.6 mA/cm²*	A, C	–/Y	1 mV MEP w/25–30% contraction	10 *Abs cSP*
Short interval cortical inhibition (SICI) and intracortical facilitation (ICF)						
Siebner et al.0 (2004)	8	10 min	A, C	–/–	Test Pulse: 1 mV MEP Cond. Pulse: 80% aMT	15
Nitsche et al. (2004)	6	11 min	A	–/–	Test Pulse: 1 mV MEP Cond. Pulse: 70% aMT	15
Quartarone et al. (2005)	8	10 min	A, C, S	–/–	Test Pulse: 0.8–1 mV MEPCond. Pulse: 80% aMT	15
Nitsche et al. (2005)	12	9 min C/13 min A	A, C	–/–	Test Pulse: 1 mV MEP Cond. Pulse: 70% aMT	15
Boros et al. (2008)	8	13 min	A	–/–	Test Pulse: 1 mV MEP Cond. Pulse: 70% aMT	12
Di Lazzaro et al. (2012)	30	20 min	C	–/–	Test Pulse: 1 mV MEP Cond. Pulse: aMT – 5% MSO	5
Batsikadze et al. (2013/*x2*)	9 (x1)8 (x1)	20 min (x1)	C (x1)S (x1)	–/–	Test Pulse: 1 mV MEP Cond. Pulse: 70% aMT	15

General notes: DB=double-blind experimental design with regards to tDCS condition (not any included pharmacological arm); NN=neuronavigation system used to guide TMS; *T*(*x*)=time (in minutes) post stimulation that measurements were reported and pooled for this analysis. A=anode; C=cathode; S=sham; Rel cSP=relative cortical silent period; Abs cSP=absolute cortical silent period.
rMT and aMT Notes: Alonzo et al. (2012), Batsikadze et al. (2013), Cambieri et al. (2012), Hasan et al. (2013), Mordillo–Mateos et al. (2012), Schmidt et al. (2013), Simis et al. (2013), and Thirugnanasambandam et al. (2011) were excluded from analysis as they did not supply numerical data.
cSP notes: Thirugnanasambandam et al. (2011), Batsikadze et al. (2013), and Hasan et al. (2013) were excluded from analysis as they did not supply discernable numerical data. However, each of these papers reported no significant change in cSP due to stimulation.
SICI and ICF notes: two studies from Munneke et al. (2011) were excluded from analysis for reporting SDs above 100%. Thirugnanasambandam et al. (2011) was excluded from analysis for reporting only percent change (rather than percentage of unconditioned response). Simis et al. (2013) was excluded from analysis as they did not supply numerical data (although this paper reported no significant effect of stimulation on either SICI or ICF). Jefferson et al. (2009) was excluded from analysis as they did not supply numerical data (although this paper reported no significant effect of stimulation on either SICI or ICF).

3.4.3. *Oscillation frequency characteristics: during picture tasks*

2 studies have explored the effect of tDCS on EEG oscillatory power during picture naming tasks using comparable protocols (Table 18); unfortunately, as both only explored anodal stimulation, we will be unable to discuss the effects of cathodal stimulation. (Wirth et al., 2011) reported no significant changes in power across any frequency following anodal stimulation during a neutral valence picture naming task (compared to sham). Similarly, (Maeoka et al., 2012) reported no significant changes in power across any frequency following anodal stimulation during either neutral or positive valence picture viewing tasks (compared to sham). However, these researchers did report a significant reduction in beta and increase in alpha band power (compared to sham) during an unpleasant valence picture viewing task (Table 19).

Table 10
Numerical values for low-density, long duration tDCS on rMT and aMT values.

		N	Mean (% of baseline)	SD	95% *u* confidence interval
Resting motor threshold (rMT)					
T0	Cathode	73	1.15	16.94	$-2.736 < u < 5.036$
	Anode	37	0.22	12.41	$-3.779 < u < 4.219$
	Sham	8	0	14	$-11.681 < u < 11.681$
Active motor threshold (aMT)					
N			**Mean (% of baseline)**	**SD**	**95% *u* confidence interval**
T0	Cathode	71	0.99	14.26	$-2.327 < u < 4.307$
	Anode	41	−1,76	10.24	$-4.894 < u < 1.374$
	Sham	8	0	13	$-10.847 < u < 10.847$

[a]Difference between either stimulation condition and sham.
[b]Difference between stimulation conditions.

3.5. *fMRI results*

3.5.1. *Short-duration stimulation (1–7 min)*

2 studies have explored the effect of very-short-duration and/or short-duration stimulation over M1 on voxel activation/spread under the active electrode during an active motor task (Table 20). Although each utilized a slightly different protocol, neither reported a significant change in either measure following either anodal or cathodal stimulation (Table 21).

Table 11
Numerical values for long duration tDCS on cSP duration.

		N	Mean (% of baseline)	SD	95% *u* confidence interval
Cortical silent period (cSP)					
T0	Cathode	34	3	27.49	$-6.240 < u < 12.240$
	Anode	16	−6.75	19.02	$-16.878 < u < 3.378$
	Sham	6	0	35	$-36.722 < u < 36.722$

[a]Difference between either stimulation condition and sham.
[b]Difference between stimulation conditions.

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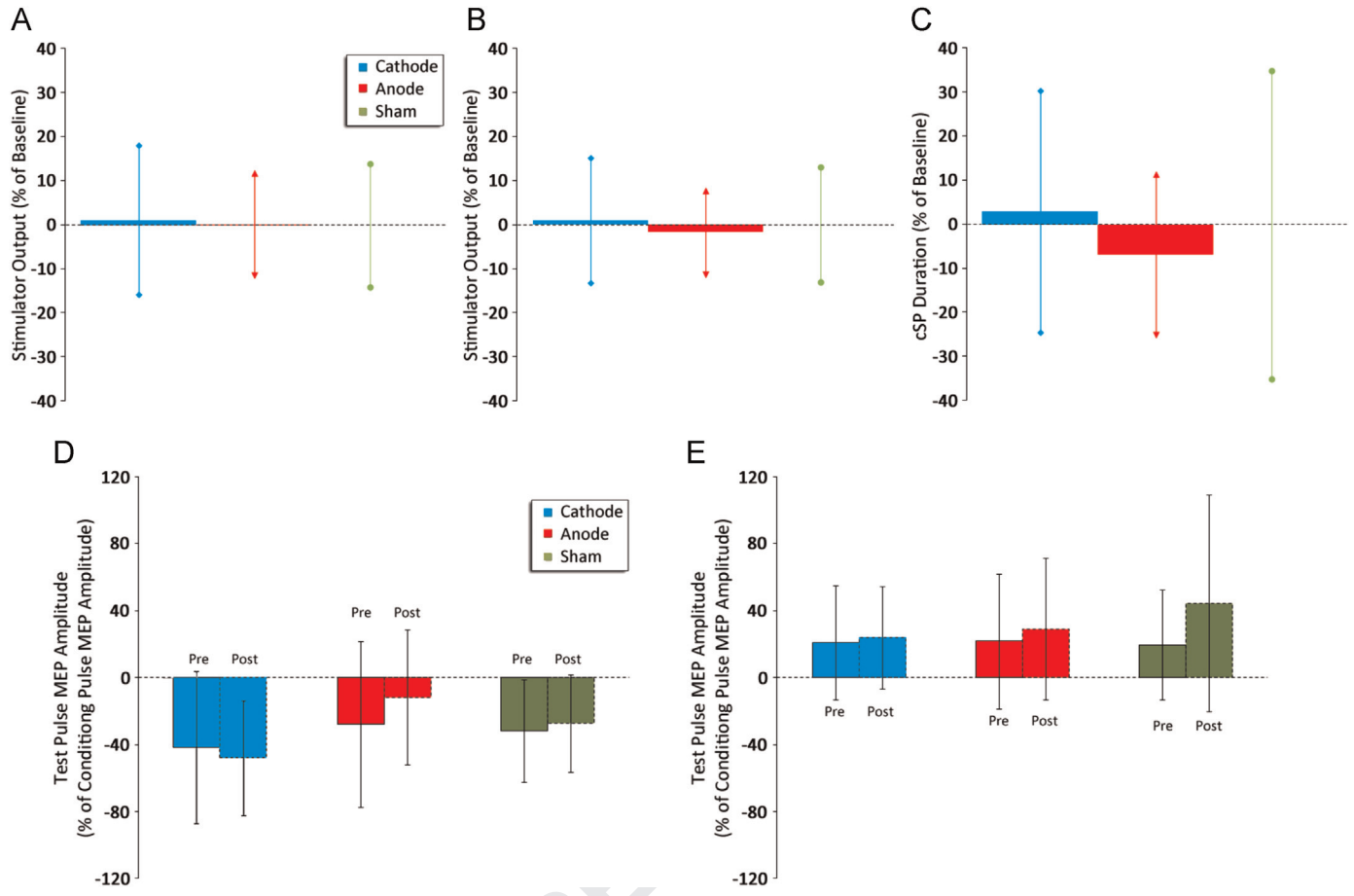

Fig. 3. Effects of tDCS on various TMS outcome measures. (A and B) Low-density, long duration (> 7 min) tDCS exploring resting and active motor thresholds, respectively; (C) long-duration tDCS exploring cortical silent period duration; (D and E) low-density, long duration tDCS exploring short interval cortical inhibition and intracortical facilitation, respectively. Error bars: ±1 SD.

3.5.1.1. Long-duration stimulation (> 7 min). 2 studies have explored the effect of long-duration cathodal stimulation over M1 on voxel activation/spread under the active electrode during an active motor task (Table 20). Neither reported any significant change in either measure. 3 studies have explored these measures following anodal stimulation. One study reported a significant increase in activation and spread whilst the other two reported no significant change in either measure following stimulation (Table 21).

Table 12
Numerical values for low-density, long duration tDCS on SICI and ICF.

			N	Mean (% of baseline)	SD	95% *u* confidence interval
Short interval cortical inhibition (SICI) and intracortical facilitation (ICF)						
SICI 2, 3, 4, and 5 ms ISI	Cathode	Pre	67	−40.69	44.05	−51.238 < *u* < −30.142
		Post	67	−46.78	33.45	−54.790 < *u* < −38.77
	Anode	Pre	42	−27.61	49.59	−42.608 < *u* < −12.612
		Post	42	−11.67	40.32	−23.864 < *u* < 0.524
	Sham	Pre	16	−31.88	30.65	−48.201 < *u* < −15.559
		Post	16	−27.38	29.13	−42.892 < *u* < −11.868
ICF 7, 9, 10, 12, and 15 ms ISI	Cathode	Pre	67	20.93	33.96	12.798 < *u* < 29.062
		Post	67	23.99	30.44	16.701 < *u* < 31.279
	Anode	Pre	42	21.93	40.24	9.760 < *u* < 34.100
		Post	42	29.12	42.26	16.339 < *u* < 41.901
	Sham	Pre	13	19.69	32.90	−0.202 < *u* < 39.582
		Post	13	44.54	64.67	5.439 < *u* < 83.641

[a]Difference between pre- and post-stimulation.
[b]Post-stimulation score difference between either stimulation condition and sham.
[c]Post-stimulation score difference between stimulation conditions.

3.5.2. ROI: SMA activation/spread: during active motor task.
3.5.2.1. Short-duration stimulation (1–7 min). 3 Studies have explored the effect of immediate and/or short-duration anodal stimulation over M1 on voxel activation/spread at SMA during an active motor task (Table 20). One study reported a significant increase, one study reported a significant decrease, and one study reported no significant change in both measures (Table 21). 2 studies have explored these measures following cathodal. One study reported a significant decrease whilst the other reported no significant change in both measures (Table 21).

3.5.2.2. Long-duration stimulation (> 7 min). 3 Studies have explored the effect of long-duration anodal stimulation over M1 on voxel activation/spread at SMA during an active motor task (Table 20). Two studies reported a significant increase whilst one reported an insignificant decrease in both measures (Table 21). 2 studies have explored this measure following cathodal stimulation. Neither reported any significant change on either measure (Table 21).

Table 13
Studies exploring the effects of long duration (> 7 min) tDCS on varied event related potential (ERP) measures.

Paper/# of studies	*N*	tDCS duration (min)	tDCS polarities	DB	Recording electrode	# Stimuli averaged	*T*(*x*)
P100 VEP amplitude: low and high contrast stimuli							
Antal et al. (2004)	16	10 (x1)	A, C	–	Oz	50	T0 – T30
Accornero et al. (2007)	10	10	A, C	–	Oz	60	T0 – T30
Vigano et al. (2013)	11	15	A	–	Oz(High Contrast only)	600	T0
N20 SEP amplitude							
Dieckhofer et al. (2006)	10	9	A, C	–	CP3	?	T0, T20
Kirimoto et al. (2011/x2)	10 (x2)	15 (x2)	A, C, S (x1)A, C (x1)	–	CP3	300	T0, T15 – 20
N2 and P2 LEP amplitude							
Antal et al. (2008)	10	15	A, C, S	–	Cz	40	T0
Terney et al. (2008)	12 A,C, 7 S	15	C, S	–	Cz	40	T0
Csifcsak et al. (2009)	10	10	A, C, S	–	Cz	40	T0
Mu/alpha ERD: motor imagery							
Matsumoto et al. (2010)	6	10	A, C, S	–	C3 and surrounds	n/a	T0
Wei et al. (2013)	8 A, 8 S	15	A, S	–	C3 and surrounds	n/a	T0
Lapenta et al. (2013)	21	20	A, C, S	–	C3 and surrounds	n/a	T0

General notes: DB = double-blind experimental design with regards to tDCS condition (not any included pharmacological arm); *T*(*x*) = time (in minutes) post stimulation that measurements were reported and pooled for this analysis. A = anode; C = cathode; S = sham.
VEP notes: Bocci et al. (2013) reported conflicting information regarding stimulation strength and method of variability reporting. For pooling, we assumed and 1.5 mA current strength and variability reported as SEM.
SEP notes: Hansen et al. (2011) was excluded from analysis due to reporting SDs over 100%.

4. Discussion

4.1. TMS discussion

Of the six included TMS outcome measures, tDCS appears to modulate only MEP amplitude (although a significant difference was found between post-stimulation SICI scores for the cathode and anode conditions, neither of these scores differed significantly from sham nor from their own pre-stimulation levels). This finding is somewhat surprising because MEP amplitude is thought to reflect corticocortical circuit excitability, which should also influence cSP, SICI, and ICF. Indeed, in the drug literature, any given intervention will rarely modulate MEP amplitude in isolation without effecting other TMS measure (for review: Paulus et al., 2008). A comparison of temporal cohorts suggests MEP modulation has been significantly decreasing since 2000. We will further discuss MEP amplitude modulation, the utility of this measure, and what the suggested temporal decrement might mean in the general discussion. Taken together, the evidence does not support the assertion that tDCS has a consistent effect on varied TMS outcome measures beyond MEP amplitude.

4.2. ERP discussion

tDCS does not appear to modulate any of the 6 pooled ERP outcome measures. Additionally, although no discernable numerical data was available for pooling, the written descriptions within included papers suggest tDCS does not modulate an additional 9 ERP measures (P100 VEP latency: low contrast stimuli, P100 VEP latency: high contrast stimuli, N30 SEP amplitude, N30 SEP latency, N1 LEP Amplitude, N1 LEP latency, N2 LEP latency, P2 LEP latency, and LEP threshold). Taken together, the evidence does not support the assertion that tDCS has a consistent effect on varied ERP components.

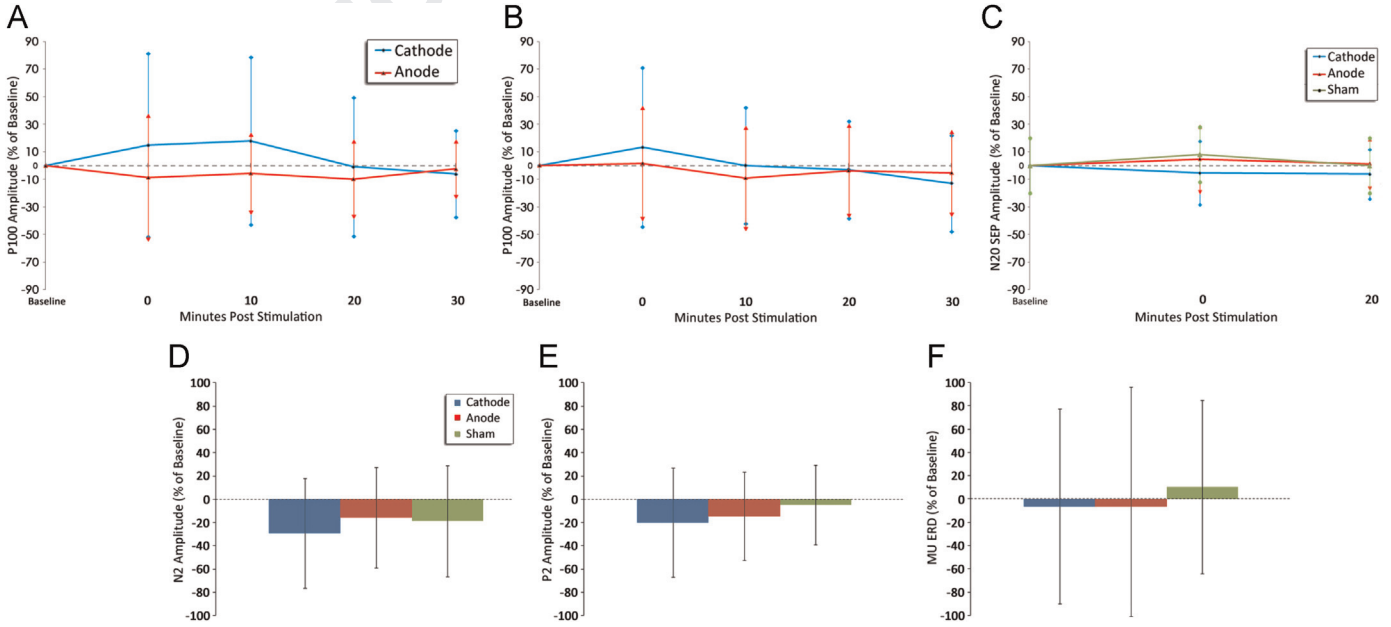

Fig. 4. Effects of tDCS on various ERP amplitude measures. (A and B) Low-density, long duration (> 7 min) tDCS exploring P100 visual evoked potential amplitude to low- and high-contrast stimuli, respectively; (C) high-density, long duration tDCS exploring N20 somatosensory evoked potential amplitude; (D and E) low-density, long duration tDCS exploring N2 and P2 laser evoked potential amplitude, respectively; (F) long duration tDCS exploring Mu/Alpha ERD. Error bars: ± 1 SD.

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Table 14
Numerical values for low-density, long duration tDCS on P100 VEP amplitude (low and high contrast stimuli).

			N	Mean (% of baseline)	SD	95% *u* confidence interval
P100 VEP amplitude: low and high contrast stimuli						
Low contrast	**T0**	Cathode	26	14.77	66.40	$-12.056 < u < 41.596$
		Anode	26	−8.62	46.40	$-27.366 < u < 10.126$
		Sham	–	–	–	–
	T10	Cathode	26	17.85	60.81	$-6.717 < u < 42.417$
		Anode	26	−5.62	29.93	$-17.717 < u < 6.467$
		Sham	–	–	–	–
	T20	Cathode	26	−0.92	50.15	$-21.181 < u < 19.341$
		Anode	26	−9.77	29.04	$-21.502 < u < 1.962$
		Sham	–	–	–	–
	T30	Cathode	26	−6.15	31.43	$-18.848 < u < 6.548$
		Anode	26	−2.46	21.85	$-11.287 < u < 6.367$
		Sham	–	–	–	–
High contrast	**T0**	Cathode	26	13.30	57.82	$-10.059 < u < 36.659$
		Anode	37	1.63	41.81	$-11.845 < u < 15.105$
		Sham	–	–	–	–
	T10	Cathode	26	0	41.91	$-16.932 < u < 16.932$
		Anode	26	−9.08	38.28	$-24.545 < u < 6.385$
		Sham	–	–	–	–
	T20	Cathode	26	−2.92	35.19	$-17.137 < u < 11.297$
		Anode	26	−3.69	34.26	$-17.531 < u < 10.151$
		Sham	–	–	–	–
	T30	Cathode	26	−13	34.73	$-27.031 < u < 1.031$
		Anode	26	−5.39	31.60	$-18.156 < u < 7.376$
		Sham	–	–	–	–

[a]Difference between either stimulation condition and sham.
[b]Difference between stimulation conditions.

Table 15
Numerical values for high-density, long duration tDCS on N20 SEP amplitude.

		N	Mean (% of baseline)	SD	95% *u* confidence interval
N20 SEP amplitude					
T0	Cathode	30	−5.33	22.96	$-13.546 < u < 2.886$
	Anode	30	4.67	25.26	$-4.369 < u < 13.709$
	Sham	10	8	18.97	$-5.557 < u < 21.557$
T20	Cathode	30	−6.17	17.95	$-12.593 < u < 0.253$
	Anode	30	1.33	19.29	$-5.573 < u < 8.233$
	Sham	10	0	22.14	$-15.823 < u < 15.823$

[a]Difference between either stimulation condition and sham.
[b]Difference between stimulation conditions.

4.3. EEG power spectrum discussion

tDCS does not appear to modulate any of the 4 pooled EEG power spectrum measures. It is possible different methodological parameters utilized in each study may have influenced this finding. However, as each included paper reported a significant finding on their respective outcome measure, one would expect to see an increased chance of finding a consistent/reliable effect. Taken together, the evidence does not support the assertion that tDCS has a consistent effect on varied EEG oscillatory power measures; though it is important to emphasize that this conclusion is drawn solely from a qualitative comparison of similar studies.

Table 17
Numerical values for long duration tDCS on Mu/Alpha ERD during motor imagery.

		N	Mean (% of baseline)	SD	95% *u* confidence interval
MU/alpha ERD: motor imagery					
T0	Cathode	27	6.48	96.23	$-31.670 < u < 44.630$
	Anode	35	6.43	83.65	$-21.283 < u < 34.143$
	Sham	35	−10.26	74.37	$-34.899 < u < 14.379$

[a]Difference between either stimulation condition and sham.
[b]Difference between stimulation conditions.

4.4. fMRI discussion

tDCS does not appear to modulate voxel activation at M1 underneath the active electrode. In addition, although tDCS does not appear to modulate voxel activation at SMA following short-duration stimulation (either polarity) or cathodal long-duration stimulation, it is difficult to conclude the effect of anodal long-duration stimulation on this measure (as 2 studies reported a similar finding and only 1 reported the opposing finding). Taken together, however, the evidence does not support the assertion that tDCS has a consistent effect on cerebral blood flow measured by fMRI; though it is important to emphasize that this conclusion is drawn solely from a qualitative comparison of similar studies.

4.5. General discussion

We quantitatively and/or qualitatively reviewed the effects of transcranial direct current stimulation on a total of 30 neurophysiologic measures across 4 different modalities. Our analysis of the literature shows that tDCS generates a significant and reliable effect on only *one* measure: MEP amplitude (Table 22). The remaining 29 measures did not reach significance or, in the case of those not amenable to pooling, displayed null or inconsistent results.

One reason why many of these measures did not reach significance may be the lack of comparable research extant in the literature. It is certainly possible that with increased data (akin to the amount reporting MEP amplitude modulation), a number of additional physiologic outcome measures will prove amenable to tDCS modulation. Future replication research is certainly encouraged to determine if this is the case.

Table 16
Numerical values for low-density, long duration tDCS on N2 and P2 LEP amplitude.

			N	Mean (% of baseline)	SD	95% *u* confidence interval
N2 and P2 LEP amplitude						
N2 amplitude	**T0**	Cathode	32	−29.06	47.33	$-45.459 < u < -12.661$
		Anode	20	−15.5	43.25	$-35.712 < u < 4.712$
		Sham	27	−18.89	47.67	$-37.789 < u < 0.009$
P2 amplitude	**T0**	Cathode	32	−19.94	47.08	$-36.252 < u < -3.628$
		Anode	20	−14.5	37.80	$-32.203 < u < 3.203$
		Sham	27	−4.96	34.27	$-18.546 < u < 8.626$

[a]Difference between either stimulation condition and sham.
[b]Difference between stimulation conditions.

Table 18
Studies exploring the effects tDCS on varied electroencephalographic (EEG) power spectrum measures.

Paper/# of studies	*N*	tDCS duration (min)	tDCS polarities	DB	Active/reference	Density (mA/cm^2)
Oscillation frequency power – at rest						
Ardolino et al. (2005)	6 C/5 S	10	C, S	–	R M1/L orbit	0.0429
Matsumoto et al. (2010)	6	10	A, C, S	–	L M1/R orbit	0.0286
Pellicciari et al. (2013)	16	13	A, C	–	L M1/R orbit	0.04
Notturno et al. (2013)	10	20	A, C, S	–	L M1/R orbit	0.0286
Oscillation frequency power (and P300 ERP) – during N-back working memory task						
Keeser et al. (2011)	10	20	A, S	Y	l dlpfc/r orbit	0.0571
Zaehle et al. (2011)	16	15	A, C	–	l dlpfc/l mastoid	0.0286
Oscillation frequency characteristics – during picture tasks						
Wirth et al. (2011)	20	37	A, S	–	l dlpfc/r shoulder	0.0429
Maeoka et al. (2012/x2)	15	20	A, S	–	l dlpfc/r orbit	0.0286

General notes: DB=double-blind experimental design with regards to tDCS condition (not any included pharmacological arm); A=anode; C=cathode; S=sham; M1=primary motor cortex; DLPFC=dorolateral prefrontal cortex.

Table 19
Summary of findings from studies exploring the effects tDCS on varied electroencephalographic (EEG) power spectrum measures.

		Gamma	Beta	Alpha	Theta	Delta
Oscillation frequency power – at rest						
Cathode	Ardolino et al. (2005)	–	–	–	–	↑
	Matsumoto et al. (2010)	–	–	–	–	–
	Pelliciari et al. (2013)	–	–	↑	↑	–
	Notturno et al. (2013)	–	–	↓	–	–
Anode	Matsumoto et al. (2010)	–	–	–	–	–
	Pelliciari et al. (2013)	–	–	↑	↑	–
	Notturno et al. (2013)	–	–	–	–	–
Oscillation frequency power – during N-back working memory task						
Anode	Keeser et al. (2011)	–	–	–	–	↑
	Zaehle et al. (2011)	–	–	–	–	–
Oscillation frequency characteristics – during picture tasks						
Anode	Wirth et al. (2011)	–	–	–	–	–
	Maeoka et al. (2012)	–	–	–	–	–
		–	↓	↑	–	–

Note: dash symbol represents no significant change.
The complete power spectrum was measured for each included study.

In addition, although MEP amplitude was the only outcome measure to achieve significance, there are a number of factors suggesting this result should be considered with caution. To begin, the majority of MEP amplitude studies in this review appear to have utilized TMS parameters that are not recognized to elicit reliable MEPs. Studies have long demonstrated large inter- and intra-subject variability of MEP amplitude; even for consecutively presented stimuli (Amassian et al., 1989; Kiers et al., 1993; Nielsen, 1996; Roth and Magistris, 2008). To enhance the reliability of this measure, practitioners have argued that MEPs should be generated using a minimum TMS intensity of 130% rMT with a 6–10 s pause between each pulse (Brasil–Neto et al., 1992; Kiers et al., 1993). A look at Table 1 reveals that at least 71 included studies (out of 79) utilized a TMS intensity below the recommended 130% rMT (0.5–1 mV MEP amplitude equates to ~115–125% rMT) and at least 50 included studies delivered TMS pulses quicker than the recommended 6–10 s ISI (0.25 Hz=one pulse every 4 sec). Furthermore, it is worth noting human and animal research suggests that using 'stronger' TMS pulses increases the number and complexity of generated corticospinal volleys (Di Lazzaro et al., 2004; Ziemann and Rothwell, 2000; Amassian and Cracco, 1987). Pharmacological research suggests that later corticospinal volleys (not generated by lower intensity TMS) are more easily effected by and reflective of cortical excitability (specifically glutamatergic and GABAergic processes; for review: Paulus et al., 2008; also see Table S2 for a list of tDCS studies exploring the effects of tDCS on neurotransmitter concentration). In fact, in a recent study, Lang et al. (2011) reported that tDCS effects are largest and most apparent in these later corticospinal volleys. Accordingly, the use of weaker TMS pulses to probe MEP amplitude modulation following tDCS may not only hinder reliability, but also may not completely probe the proposed mechanisms of change following stimulation.

Additionally, as noted above, the effects of tDCS on MEP amplitude have been significantly *diminishing* over recent years (most notably for anodal stimulation). Technological (both tDCS and TMS) and methodological advances since 2000 are likely to have reduced levels of noise which should, in turn, increase the reliability of outcome measures. The fact that MEP amplitude effects have been diminishing with these advances suggests that the efficacy of tDCS may not be the sole explanation for changes in MEPs in the studies included in this review.

It is possible that varying stimulation durations could account for the decrease in MEP amplitude effects since 2000. On average, more recent long-duration protocols have utilized a stimulation duration approximately 5 min longer than earlier studies (*2000–2004*=10.50 min; *2005–2009*=10.62 min; *2010-Present*=15.32 min). According to the meta-plastic homeostatic theory (see Siebner et al., 2004; Fricke et al., 2011), longer-duration stimulation should, in fact, reduce the modulatory response. However, our analysis also revealed a decrease in response for both very-short and short-duration protocols. Therefore, duration effects are unable to account for the complete diminution pattern we found. Furthermore, as the number of studies which included a double-blind protocol and/or utilized neuronavigation to guide TMS does not markedly vary between temporal cohorts, these paradigmatic consideration are also unable to account for this pattern.

In a recent review paper, this research group pointed out five-major issues related to current tDCS research: namely, inter-subject variability, intra-subject reliability, sham/blinding conditions, motor/cognitive interference, and electric current influences (Horvath et al., 2014). Each of these issues may provide potential explanations for the results obtained here. Regarding inter-subject variability, it is possible that many tDCS effects are unique to the individual being stimulated and, accordingly, these effects have been diminished or lost in pooled data. If this is the case, future experimentation exploring individualized response may better elucidate the efficacy and reliability of tDCS than a systematic review, such as this one. In addition, lack of accounting for hair thickness (a non-conductive barrier between tDCS and the head), individual neural architecture, and current flow dynamics may greatly influence tDCS effects which, in turn, may have influenced our findings. As noted above, some groups are now beginning to account for these effects. It is likely that the future adaptation of tDCS protocols to each individual may lead to a more

Table 20
Studies exploring the effects tDCS on varied functional magnetic resonance imaging (fMRI) measures.

Paper (# of studies)	*N*	tDCS duration	tDCS Polarities	DB	Active/ reference	Current density (mA/cm^2)	Task	Compare	Analysis notes
ROI: M1 activation/spread – during active motor task: short-duration									
Baudewig et al. (2001)	6	5 min	A, C	–	L M1/R orbit	0.04	Finger tapping	Pre- to post-stim	r:COA=$p<0.001$ Spread=$p<0.05$ (software: In-house)
Antal et al. (2011)	13	20 s	A, C, control	–	L M1/R orbit	0.0286	Finger tapping	Post-stim active vs control	VOI RFX: corrected threshold=q(FDR)=0.05(software: BrainVoyagerQX)
ROI: M1 activation/spread – during active motor task: long-duration									
Stagg et al. (2009b)	15	10 min	A, C, S	–	L M1/R orbit	0.0286	Sequential finger press	Post-stim active vs sham	ROI MFX: corrected threshold=$Z>2.0$, $p<0.01$(software: FMRIB)
Jang et al. (2009)	7	20 min	A, S	–	L M1/R orbit	0.0286	Grasp/release	Post-stim active vs sham	ROI RFX: uncorrected threshold=$p<0.001$ (software: SPM2)
Saiote et al. (2013)	30	10 min	A, C, S	–	L M1/R orbit	0.0286	Fist squeezing	Post-stim active vs sham	MFX: corrected threshold=$Z<2.3$, $p<0.05$(software: FEAT)
ROI: SMA activation/spread – during active motor task: short-duration									
Baudewig et al. (2001)	6	5 min	A, C	–	L M1/R orbit	0.04	Finger tapping	Pre- to post-stim	r:COA=$p<0.001$ spread=$p<0.05$ (software: In-house)
Antal et al. (2011)	13	20 s	A, C, control	–	L M1/R orbit	0.0286	Finger tapping	Post-stim active vs control	VOI RFX: corrected threshold=q(FDR)=0.05(software: BrainVoyagerQX)
Kwon and Jang (2011)	12	2 min	A, S	–	l M1/r orbit	0.0286	Grasp/release	Post-stim active vs sham	VOI RFX: uncorrected Threshold=$p<0.001$ (software: SPM8)
ROI: SMA activation/spread – during active motor task: long-duration									
Stagg et al. (2009b)	15	10 min	A, C, S	–	L M1/R orbit	0.0286	Sequential finger press	Post-stim active vs sham	ROI MFX: corrected Threshold=$Z>2.0$, $p<0.01$(software: FMRIB)
Jang et al. (2009)	7	20 min	A, S	–	L M1/R Orbit	0.0286	Grasp/release	Post-stim active vs sham	ROI RFX:Uncorrected Threshold=$p<0.001$ (software: SPM2)
Saiote et al. (2013)	30	10 min	A, C, S	–	L M1/R orbit	0.0286	Fist squeezing	Post-stim active vs sham	MFX: corrected threshold=$Z<2.3$, $p<0.05$(software: FEAT)

General notes: DB=double-blind experimental design with regards to tDCS condition (not any included pharmacological arm); ROI=region of interest; A=anode; C=cathode; S=sham; M1=primary motor cortex; r=correlation coefficient; COA=center of activation; IND=individual noise distribution; VOI=volume of interest; RFX=random effects analysis; qFDR=false discovery rate q-value; MFX=mixed-effects modelROI: M1 activation/spread: during active motor task.

Table 21
Summary of findings from studies exploring the effects tDCS on varied functional magnetic resonance imaging (fMRI) measures.

		Peak voxel activation	Cluster size (# of voxels)
M1 activation – during active motor task: short-duration			
Cathode	Baudewig et al. (2001)	–	–
	Antal et al. (2011)	–	–
Anode	Baudewig et al. (2001)	–	–
	Antal et al. (2011)	–	–
M1 activation – during active motor task: long-duration			
Cathode	Stagg et al. (2009a, 2009b)	–	–
	Saiote et al. (2013)	–	–
Anode	Jang et al. (2009)	–	–
	Stagg et al. (2009)	↑	↑
	Saiote et al. (2013)	–	–
SMA activation – during active motor task: short-duration			
Cathode	Baudewig et al. (2001)	↓	↓
	Antal et al. (2011)	–	–
Anode	Baudewig et al. (2001)	–	–
	Antal et al. (2011)	↓	↓
	Kwon and Jang (2011)	↑	↑
SMA activation – during active motor task: long-duration			
Cathode	Stagg et al. (2009a, 2009b)	–	–
	Saiote et al. (2013)	–	–
Anode	Jang et al. (2009)	↑	↑
	Stagg et al. (2009a, 2009b)	↑	↑
	Saiote et al. (2013)	–	–

Note: dash symbol represents no significant change.

Table 22
Summary of the effect of tDCS on each neurophysiological outcome measure explored in this systematic review.

Numerically analyzable outcome measures	
tDCS outcome measure (modality)	**Significant effect**
MEP amplitude (TMS)	Yes
Resting motor threshold (TMS)	No
Active motor threshold (TMS)	No
Cortical silent period (TMS)	No
Short interval cortical inhibition (TMS)	No
Intracortical facilitation (TMS)	No
P100 visual evoked potential amplitude – low contrast stimuli (ERP)	No
P100 visual evoked potential amplitude – high contrast stimuli (ERP)	No
N20 somatosensory evoked potential amplitude (ERP)	No
N2 laser evoked potential amplitude (ERP)	No
P2 laser evoked potential amplitude (ERP)	No
MU event related displacement (ERP/EEG power spectrum)	No
Non-numerically analyzable outcome measures	
tDCS outcome measure	**Consistent effect**
P100 visual evoked potential latency – low contrast stimuli (ERP)	No
P100 visual evoked potential latency – high contrast stimuli (ERP)	No
N30 somatosensory evoked potential amplitude (ERP)	No
N30 somatosensory evoked potential latency (ERP)	No
N1 laser evoked potential amplitude (ERP)	No
N1 laser evoked potential latency (ERP)	No
N2 laser evoked potential latency (ERP)	No
P2 Laser Evoked Potential Latency (ERP)	No
Laser evoked potential threshold (ERP)	No
Oscillatory frequency power at rest (EEG power spectrum)	No
Oscillatory frequency power during N-back task (EEG power spectrum)	No
P300 potential amplitude during N-back task (ERP/EEG power spectrum)	No
P300 potential latency during N-back task (ERP/EEG power spectrum)	No
Oscillatory frequency power during picture tasks (EEG power spectrum)	No
M1 activation during active motor task – short duration stimulation (fMRI)	No
M1 activation during active motor task – long duration stimulation (fMRI)	No
SMA activation during active motor task – short duration stimulation (fMRI)	No
SMA activation during active motor task – long duration stimulation (fMRI)	No

comprehensive and consistent view of tDCS effects.

Finally, the lack of sham-controlled, double-blind, and neuronavigation-guided (NN) TMS studies is somewhat alarming. Of 106 TMS studies included in the analysis, only 18 included a sham/control condition, only 7 utilized a double-blind study design, and only 5 reported using NN to guide TMS delivery. Although the lack of studies using NN may be understandable (as the technology is rather novel), it is worth noting that growing body of evidence demonstrates that NN allows for millimeter precision whilst "standard" TMS positioning can engender significant inter-pulse coil movement (see Gugino et al., 2001; Schönfeldt–Lecuona et al., 2005; Sparing et al., 2008; Sack et al., 2009;) In fact, Ahdab et al. (2010) have argued that the inaccuracy of non-NN TMS is so great that results obtained using "standard" positioning techniques should be interpreted with caution. The lack of studies utilizing a double-blind paradigm may also be somewhat understandable, as research has demonstrated it is quite difficult to blind the tDCS practitioner, especially if he/she is the same person delivering TMS or setting up EEG electrodes (a necessity in many smaller research groups: O'Connell et al., 2012). However, the lack of studies including a sham condition is harder to understand as this is clearly established scientific best-practice. Future research would benefit from the inclusion of a sham condition, blinding of both the participant and experimenter to the tDCS condition being utilized, and employment of modern frameless stereotactic NN systems (when utilizing TMS) to ensure all results are accurate and unbiased.

4.6. Limitations

A major limitation of this systematic review is the lack of comparable research extant in the literature. Beyond the many neurophysiological outcome measures in the literature not explored by at least two different research groups (see Table S1 in Supplementary material), many replicated outcome measures have utilized different values of the four adjustable tDCS parameters (electrode location, current density, stimulation duration, and stimulation-to-task relationship). Due to this variability, there simply is a dearth of meaningfully comparable tDCS studies. It is certainly possible that, with increased data, a number of additional measures (beyond MEP amplitude) will reach significance. As this field evolves, it may be beneficial to consider standardized protocols and attempt to directly replicate work already in the published literature.

Another limitation concerns the inability to derive a meaningful effect size from the neurophysiological data. As noted in the introduction, the majority of neurophysiological studies included in this review did not use a control or sham condition; rather, many simply compared either varied active stimulation protocols or pre- and post-active stimulation measures (for comment: Horvath et al., 2014). Due to an inability to derive meaningful effect sizes, we were unable to conduct a true meta-analysis. Accordingly, the quantitative analyses used in this systematic review (derived from weighted means and pooled standard deviations) must be interpreted with caution. It is certainly possible that, had it been feasible to derive meaningful effect sizes, a number of

measures may have reached significance. Again, as this field evolves, it may be beneficial to include effective control conditions in every study so that the effects of stimulation can be differentiated from natural neurophysiological fluctuation and a more accurate effect of stimulation can be determined.

Along similar lines, a number of papers included in this systematic review were not amenable to pooling due to no hard-data being apparent in the final publication/s (either in the form of numerical tables or graphs). It is possible, had all researchers included hard-numbers (even for measures that did not reach significance in the original study), a number of outcome measures may have reached significance in this review. Accordingly, future researchers should be encouraged to include discernable data so that future analyses can include more data and develop a more accurate picture of tDCS effect.

Another limitation of this study is its exclusion of data obtained in non-healthy adult populations. There is a large body of work exploring the neurophysiologic effects in clinical populations (for review: Brunoni et al., 2012), elderly population (e.g. – Berryhill and Jones, 2012; Kar and Wright, 2014), and animal models (for review: Brunoni et al., 2012). Accordingly, the results and conclusions reported in this paper cannot and should not be extrapolated to these other groups.

Finally, there is a rather robust literature suggesting tDCS can modulate cognitions and performance on a number of behavioral tasks. Although the lack of significant neurological effects found in this review may raise questions concerning the mechanisms by which tDCS modulates behavior, it does not speak directly (positively nor negatively) to behavioral modulation itself. As such, it would be a mistake to extend the findings of this analysis to the whole of the tDCS literature; rather, similar, robust systematic reviews of the cognitive and behavioral data are necessary before far reaching comments about this device can be made. This group has undertaken such reviews and the manuscripts are currently in preparation.

5. Conclusion

In the end, tDCS does not appear to generate a reliable neurophysiologic effect. Although MEP amplitude does appear to be sensitive to tDCS modulation, this effect has been significantly decreasing since 2000 and other, more reliable TMS measures believed to rely on similar neural mechanisms (e.g. SICI, ICF, and cSP) have all shown no effect to tDCS. These findings raise questions about the mechanistic framework of tDCS. If future research continues to generate evidence consistent with the conclusion that tDCS generates little-to-no reliable neurophysiological effect, it will be important to begin reconsidering the current mechanistic foundations used to explain the effects of tDCS. It is hoped that greater consistency in the utilization of stimulation protocols, the use of sham conditions, and the statistical reporting of all outcome measures assessed (regardless of significance) will allow for a more comprehensive assessment of the utility of tDCS in the future.

Uncited references

Cogiamanian et al. (2007), Kidgell et al. (2013b), Madhavan and Stinear (2010) and Rosler et al. (2008).

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuropsychologia.2014.11.021.

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